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DOUBLE-CONTRAST CYSTOGRAPHY IN TUMORS OF THE URINARY BLADDER

by

OSBORNE BARTLEY and CARL GUSTAF HELANDER

Various contrast media, both opaque and gaseous, may be used, either singly or in combination, in the roentgen examination of the urinary bladder. The commonest are watersoluble iodine salts; gas alone or in conjunction with opaque media (double contrast) has been employed, to judge from the literature only on a minor scale (KNEISE & SCHOBER 1941, GRAAS & MILLER 1957, and others). The limited use of gas as a contrast medium is probably due to the fact that several deaths from gas embolism have been reported (CAMPBELL 1951).

We have found that tumors of the bladder often cannot be satisfactorily evaluated, and in some cases cannot even be demonstrated, with the use of a single contrast medium, whether it be opaque or gaseous, no doubt because of an insufficient difference in density between the tumor and the contrast medium. A vesical tumor is more likely to be shown if two contrast media of different densities are employed and we have therefore for bladder examinations adopted a double-contrast method which has been modified in several respects from those previously employed. We now use carbon dioxide in place of oxygen as a negative contrast medium; CO_2 is absorbed thirty times more readily than O_2 in plasma (BEST & TAYLOR 1945) and we feel that its use has eliminated

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From Roentgen Department I (Director: Prof. S. R. Kjellberg) and Roentgen Department II (Director: Docent I. Wickbom), Sahlgrenska Sjukhuset, Gothenburg, Sweden.

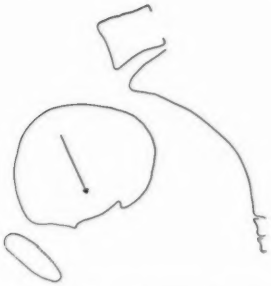

Fig. 1. Relation between the base of the bladder and pelvic inlet. Arrow shows the beam direction perpendicular to the base; the patient consequently had to be semi-recumbent.

Fig. 2. Normal case, axial view. Opaque medium has collected at base of bladder, in and around the trigone; The internal meatus (←) and ureteric ridges (↔) are seen. The left ureteric orifice (←○) is shown by the accumulation of contrast medium.

the deleterious effects of any possible gas embolism. The carbon dioxide remains in the bladder long enough for the examination to be completed. It is essential to use an opaque medium which readily adheres to the mucosa. We have tried several different agents such as Umbradil (Astra), Urografin (Schering), and Hypaque (Winthrop), as well as viscous contrast media, and so far have found Dionosil aqueous (Glaxo) to be the best.

Technique

A Nelaton catheter is inserted in the urinary bladder and the latter is emptied. Eight to 10 ml Dionosil aqueous (Glaxo; 50 per cent suspension of propyliodine) are then injected with the patient supine. This is followed by the injection of CO_2 through the catheter until the patient experiences a desire to empty the bladder, generally when 200 to 300 ml gas have been introduced. The opaque contrast medium forms a coating on the mucosa which contrasts with the gas. Normally the mucous membrane in a bladder distended with gas is smooth or slightly rugose. Neoplasms, especially those which are papillomatous, have a more irregular surface; for this reason small tumors are generally quite distinct in the cystogram, even without tangential views. If opaque contrast medium alone is used, tangential views, as EDLING (1952) pointed out, will be required for the detection of small tumors. Therefore, in order that the opaque contrast medium may come into contact with the whole of the vesical mucosa the patient is rotated after the injection of the contrast media.

The conditions most favourable for the demonstration of tumors will be present when the latter are situated in the gas layer. Urine passes into the

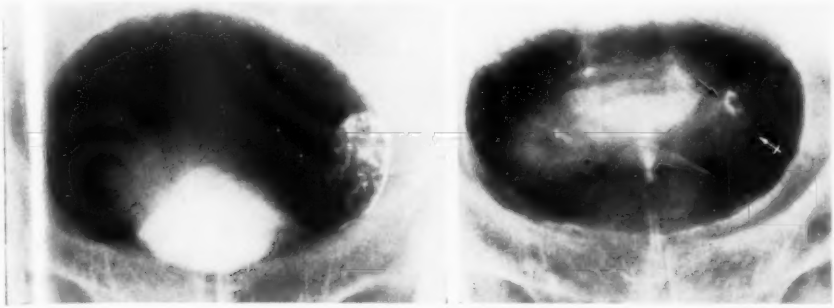

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Fig. . Vesical papilloma and prostatic hypertrophy. a) Prone. The bulk of the papilloma, situated poste iorly, is well shown because contrast medium has collected between the papillae, and the tumor is sur ounded by gas. b) Supine. Only a small part of the tumor is now outlined by gas (←) and has a coatin of opaque medium. In the anterior lateral part of the base of the bladder is a small contrast defec caused by the tumor (↔). Compare the smooth, regular mucosal surface of the prostatic adenoma with that of the papilloma.

bladder throughout the examination and collects in its lowermost parts; it does not mix either with the gas or, as a rule, with the opaque contrast medium. The admixture of urine can be reduced, it is true, by compression of the ureters, but will not be prevented entirely. This source of error is eliminated by taking films with the patient both prone and supine; right and left laterals are also desirable. Exposures should be made with both horizontal and vertical projections in each position, and oblique views are also advisable. Contrast medium, which fails to adhere to the bladder wall, collects in the most dependent part. Provided the coating of opaque medium is not too thick, neoplasms may be discernible as defects in the positive contrast.

For a satisfactory investigation of the base of the bladder, a special additional projection is required. Since the plane of the base is roughly parallel with the pelvic inlet, an axial view of the latter is taken perpendicular to the base (Fig. 1), with the patient semirecumbent and the beam vertical.

The double-contrast method makes it possible to study in various ways the topographic anatomy of the base of the bladder (Fig. 2) and the relation of tumors to the different anatomical structures. This is effected either by obtaining films with the patient in such a position that the gas contrasts with the base of the bladder, or so that tumors are discernible as defects in the positive contrast coating.

The number of films required for a complete examination is approximately twelve. It has therefore been necessary to investigate the roentgen dose to which

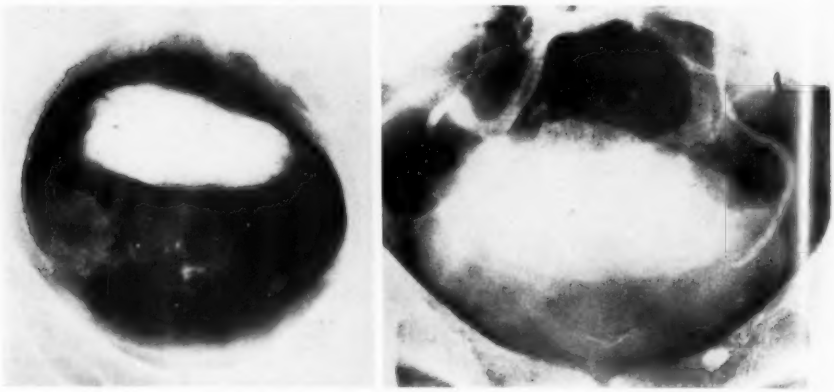

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Fig. 4. Two finely papillomatous tumors, one of them situated in the anterior part of the trigone. a) Axial view. b) Contrast filling of the bladder at urography. Although the tumors are relatively large, they are not well shown. The ureteric orifices are not involved.

the gonads are exposed. This part of the investigation was kindly conducted for us by Dr. LARSSON who used the method he has previously reported (1958).

The testicular dose was determined by means of ionization chambers placed on the scrotum, the ovarian dose with the aid of chambers inserted in the rectum. Five patients were examined. In 4, the total testis dose varied between 140 and 225 mr; the corresponding figures for the ovary were 1 725 to 1 950 mr. The total testis dose in one patient was found to be approximately 3 000 mr due to the fact that in some exposures the scrotal ionization chambers were subjected to unattenuated primary radiation. This case demonstrates the importance of the careful use of diaphragms. Granted this, the gonad dose does not appear to be so great as to constitute a contra-indication from the genetic standpoint, the more so in that most of the patients with bladder growths are of relatively advanced age, and the annual number of examinations per patient is small.

Films of adequate contrast are essential for the satisfactory demonstration of neoplasms. Our exposure data were as follows: a Bucky grid was used for all exposures with a vertical beam direction and a stationary grid built into a cassette for those with a horizontal beam. The FFD were 95 cm and 100 cm, respectively. For the p.a., a.p. and oblique views, with the beam vertical, the voltage was approximately 70 kV, the current 200 mA, and the mAs value around 140; for the lateral and axial views the corresponding figures were about 100 kV, 200 mA, and 280 mAs, and about 80 kV, 200 mA, and 280

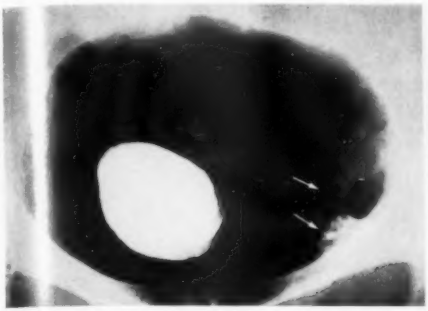


Fig. Prone. Two papillomas in left posterior part of bladder: a larger one with accumulation of contrast medium between the papillae, and a smaller one about the size of a grain of rice.

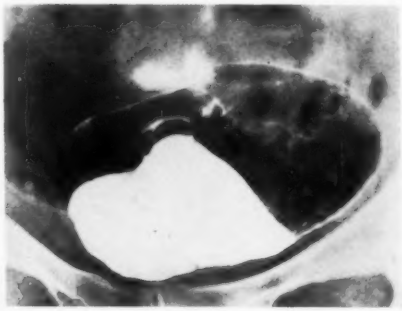


Fig. 6. Prone. Papillomatosis, the tumors ranging in size from grains of rice to the size of half a hazelnut.

mAs, respectively. With a horizontal beam the figures were approximately 50 kV, 200 mA, and 140 mAs for the a.p. and p.a. views, and about 90 kV, 200 mA, and 140 mAs for the lateral views.

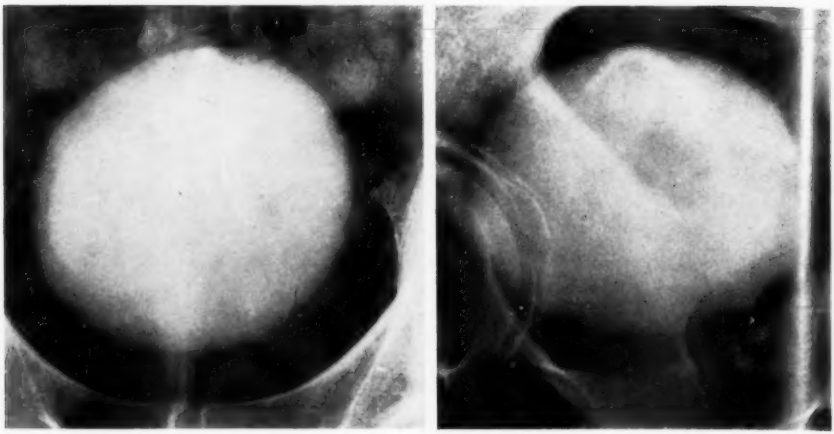
Results

Our series comprises 75 double-contrast cystographies referable to the period November 1958 to May 1959. Twenty of them were in verified cases of bladder tumors; the remainder were in cases of other morbid conditions, such as hypertrophy or carcinoma of the prostate, cystitis, diverticula, vesical calculi, etc.

The tumor or tumors were clearly discernible in all cases. In some cases of multiple growths, tumors which had been overlooked at the initial cystoscopy were demonstrable. Papillomatous tumors are easiest to show since they have very irregular surfaces and the opaque medium collects between the papillae (Figs 3 and 4). Even tumors no larger than grains of rice were shown distinctly in the cystograms, although the views were not tangential (Figs 5 and 6). It is possible, however, that small polypoid growths with smooth surfaces will not be demonstrable without tangential views.

The double-contrast method has proved definitely superior to cystography with a single contrast medium (Fig. 7); tumors can be satisfactorily demonstrated and evaluated even in cases in which depression of the pelvic floor makes a free projection from the pelvic bones difficult (Fig. 8).

That the position of the tumor in relation to the gas is of fundamental importance is illustrated by Figs 3, 4a, 5, 6, and 8b. Tumors growing into the base of the bladder may be localized either because they produce a defect in the



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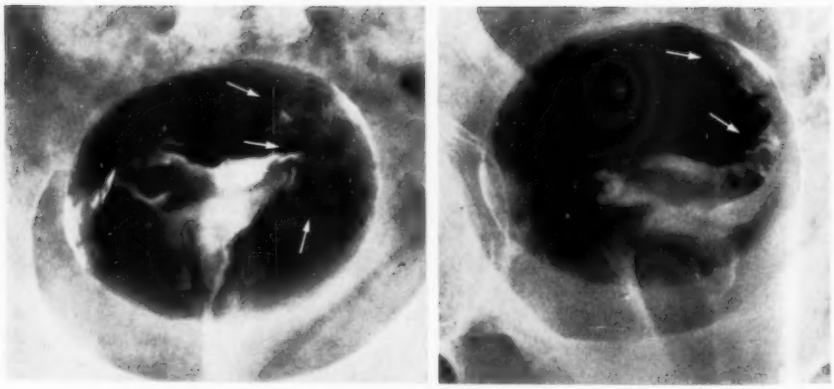

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Fig. 7. Carcinoma, posteriorly on the left side. a) and b) Cystography with Umbradil appro 2 %. c) and d) Double-contrast examination in corresponding projections. The irregular, kidney aped tumor is clearly demonstrated at the latter examination (←), but is not fully visible in (a) 1 (b). On the right is a defect at the site of the ureteric orifice, possibly a blood clot.

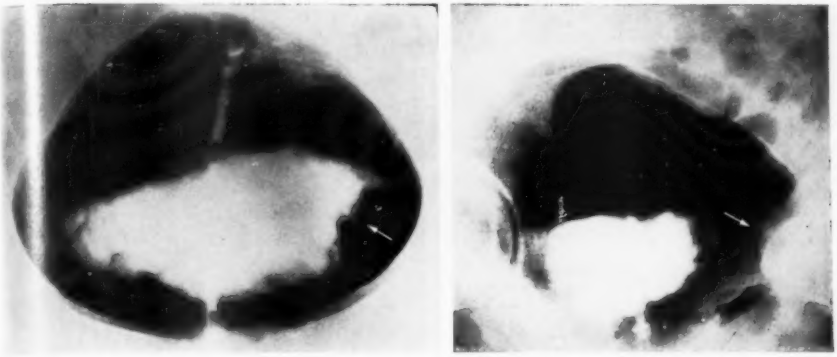

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Fig. 8. Papilloma. a) Supine. The tumor produces a contrast defect in the left lateral part of the base of the bladder (←). b) Prone. It is now surrounded by gas and discernible by its coating of contrast medium, although there is no free projection from the pelvic bones.

positive contrast (Figs 8a, 9 and 10), or because they become coated with opaque medium (Fig. 4a).

The aim of the cystographic examination is not merely to demonstrate and localize the tumors, but also if possible to determine their nature. FRANKSSON, LINDBLOM & WHITEHOUSE (1956) have shown that the cystographic appearance

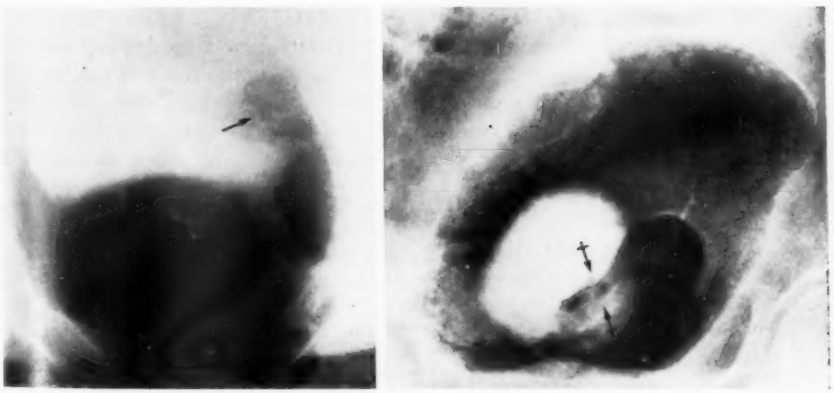

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Fig. Carcinoma of left posterior region of base of bladder. a) Axial view. At the site of tumor (←), an irregular contrast defect to the left in the retro-ureteric fossa is evident. b) Supine, right side raised. The tumor is growing round the ureteric ridge (↔).

a b

Fig. 10. Prostatic carcinoma. a) Axial. b) Right anterior oblique. The tumor (←) infiltrates central part of trigone without involving the ureteric orifices (↔) or the internal meatus.

of a neoplasm is an important factor in the evaluation of its degree of malignancy. For instance, tumors having ill-defined contours are more malignant than sharply limited growths. Solid tumors are usually more malignant than those of the papillomatous type, and sessile neoplasms more so than those with slender pedicles. Since there is a far greater difference in contrast between the coated surface of a tumor and gas than between a tumor and an opaque medium alone, the degree of malignancy probably can be evaluated better by double-contrast cystography. There is, however, one possible exception. In some of our cases a pedunculated tumor gave the impression of being sessile; this was probably because the bulk of the tumor enshrouded and concealed the relatively short pedicle. No complications have been observed in the 75 cases investigated by this method.

SUMMARY

Twenty cases of verified bladder tumors have been examined by a modified double-contrast method. Its value lies in the possibility of determining the relation of tumors to the base of the bladder, in permitting demarcation of even very small tumors without tangential views, and in facilitating evaluation of the degree of malignancy.

ZUSAMMENFASSUNG

Zwanzig Fälle von verifizierten Blasentumoren wurden mit einer modifizierten Doppelkontrastmethode untersucht. Der Wert der Methode liegt darin, dass es damit möglich ist, die Beziehung des Tumors zur Basis der Blase zu bestimmen, dass die Darstellung auch sehr kleiner Tumoren ohne Tangentialprojektion gelingt und die Bestimmung des Malignitätsgrades erleichtert wird.

RÉSUMÉ

Les auteurs ont examiné vingt cas de tumeurs vésicales vérifiées par une méthode en double contraste modifiée. Son intérêt réside dans la possibilité de déterminer les rapports des tumeurs avec la base de la vessie en permettant de délimiter même de très petites tumeurs sans utiliser des projections tangentielles et en facilitant l'appréciation du degré de malignité.

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FROM THE ROENTGEN INSTITUTE (DIRECTOR: PROF. G. G. PALMIERI) OF THE UNIVERSITY OF BOLOGNA, ITALY

LEFT CARDIAC VENTRICULOGRAPHY BY MEANS OF PERCUTANEOUS CATHETERIZATION OF A FEMORAL ARTERY IN THE DIAGNOSIS OF MITRAL INSUFFICIENCY

by

G. Tori and G. F. Garusi

The surgical treatment of mitral stenosis requires the pre-operative recognition of the existence and of the degree of regurgitation through the mitral orifice.

Modifications of the atrial volume during the ventricular systole have been studied and used as a means of differential diagnosis by numerous workers (Chamberlain et coll., Elkin et coll., inter al.). However, neither fluoroscopic observation of the systolic expansion of the atrium nor the typical modifications of the electrokymographic curve, afford sufficient information for a really satisfactory pre-operative evaluation.

Angiocardiography by traditional or selective methods permits observations of the morphology and volume of the left atrium as well as of the volume of the left ventricle, which may be considered in the differential diagnosis between stenosis and mitral insufficiency.

The appearance of the mitral orifice is also of considerable significance in the differential diagnosis between stenosis and insufficiency. As has been shown by Arvidsson, a characteristic distension of the mitral cusps occurs in most cases of mitral stenosis during diastole and produces a rounded dome-shaped appearance which is called 'ballooning of the valve'. No such ballooning is seen in mitral insufficiency.

Björck et coll. and Soloff et coll. observed that the volume variations of

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th left atrium are wider in mitral insufficiency than in stenosis. ARVIDSSON w able to demonstrate that in most cases the maximal volume changes were la er in mitral insufficiency than in stenosis. It is, however, not possible to est blish any definite limits in the size of the volume changes in different fo s of mitral disease. ARVIDSSON emphasised the importance of the value of he maximal diastolic volume of the left ventricle, which is normal or sm ller than normal in pure stenosis while, obviously, it appears increased in nsufficiency. Nevertheless, there may be, even in mitral stenosis, an increase in the diastolic ventricular volume if an aortic lesion or arterial hypertension is also present; in such cases the left ventricle will be dilated though this will not necessarily be an indication of mitral insufficiency.

Angiocardiographic observations are without doubt of greater value when they are compared to those made by other roentgenologic methods, among which we would mention both tomography and roentgenkymography.

Left cardiac ventriculography has provided a more accurate method of objective assessment of the presence and degree of mitral valvular insufficiency. Eventual reflux by regurgitation from the corresponding ventricle may be demonstrated in the atrium after the contrast medium has been injected distally from the mitral valve. Under the conditions obtaining in left cardiac ventriculography with selective methods an undamaged atrio-ventricular orifice does not allow appreciable opacity of the atrium due to reflux to occur.

Transitory refluxes may, on the other hand, manifest themselves, even with undamaged valves, in the presence of functional changes in the rhythm of the heart; this has been described by STAUFFER et coll. and confirmed by DALLA ROSA et coll. This phenomenon is however a fleeting one and the refluxes are quite different from those which persist during diastole and systole in more than one heart cycle in mitral insufficiency.

Authors' method and comparison with other techniques. The first injection of contrast medium distally into the left ventricle was performed by NUVOLI by trans-thoracic puncture in 1936. PONSDOMENECH & NÚÑEZ published 30 such cases in 1951. This technique of direct trans-thoracic left ventriculography was successfully applied by SMITH et coll., NORDENSTRÖM et coll., LEHMAN et coll., and GILMAN et coll.

Left cardiac ventriculography may, however, also be effected by retrograde catheterization of the left ventricle through the aortic orifice (PRIOTON et coll., BONTE et coll., LEGRAND et coll., MOUQUIN et coll., PORSTMANN et coll., AMPLATZ et coll., TORI and GARUSI, and HANSON et coll.). The method used by us is in the main the same as that followed by these authors — except PORSTMANN et coll., AMPLATZ et coll., HANSON et coll. — and consists of percutaneous arteriography by the technique proposed by PEIRCE in 1951, and particularly by the method performed by SELDINGER (1952).

The practical introduction by ÖDMAN of opaque catheters which may be

moulded by heat has considerably facilitated the carrying out of the arterial catheterization technique so as to allow the passing of the catheter, under fluoroscopic control, as far as the left ventricle. More detailed information on the technique used by us has been reported in a previous publication, to which we would refer the reader.

Selective injection of the left ventricle by percutaneous catheterization of a femoral artery, constitutes a relatively simple and harmless procedure, especially when compared to other methods of direct trans-thoracic cardiography. The method may be easily carried out in any suitably equipped roentgen department, whereas left trans-thoracic ventriculography must be performed only in an operating theatre. In fact, this procedure is anything but free from risks; the drawbacks encountered by LEHMAN et coll. are undoubted proof of this.

Trans-thoracic puncture may provoke extrasystoles, pneumothorax, pneumopericardium, hemopericardium, and intramyocardiac haemorrhages. The greatest danger lies in the accidental intramyocardiac injection of the contrast medium when serious cardiac arrhythmias, ventricular block, and ventricular fibrillation may be caused. Only by taking the most scrupulous care in the introduction and movement of the needle can the risk of an intramyocardiac injection be reduced (LEHMAN). In babies and small children the small size of the ventricular cavity makes it most difficult to determine the exact position of the point of the needle, so that the dangers of intramyocardiac injection are increased. For this reason, as stated by LEHMAN et coll., the procedure must be considered inadvisable in these subjects.

In left cardiac ventriculography by retrograde catheterization the accidents that may occur at ventricular puncture are avoided. The passing of the catheter through the aortic valve, which is the principal difficulty of the method, is, however, possible in almost all cases when flexible catheters with suitably shaped points are employed. The danger of blocking a coronary artery or, worse still, the injection into it of large quantities of contrast medium can be avoided by careful fluoroscopic control.

No trouble in the manoeuvering of the catheter or in the injection of the contrast medium has been experienced by us or by other workers who have used the method. We have not encountered any immediate or late side-effects. The intraventricular injection does not seem to influence the electrocardiographic tracing to any great extent. The irregularities in rhythm are, however, very brief and disappear soon after the injection of the contrast medium.

Serial roentgenograms (at least 4 to 6 films per sec for periods of 4 to 5 sec) in two projections are obtained. The lateral view is the better of the two for determining the presence of endoatrial regurgitation. The frontal view offers less information on the dynamics of the mitral valve, but supplies valuable data on the morphology and dynamics of the left ventricle.

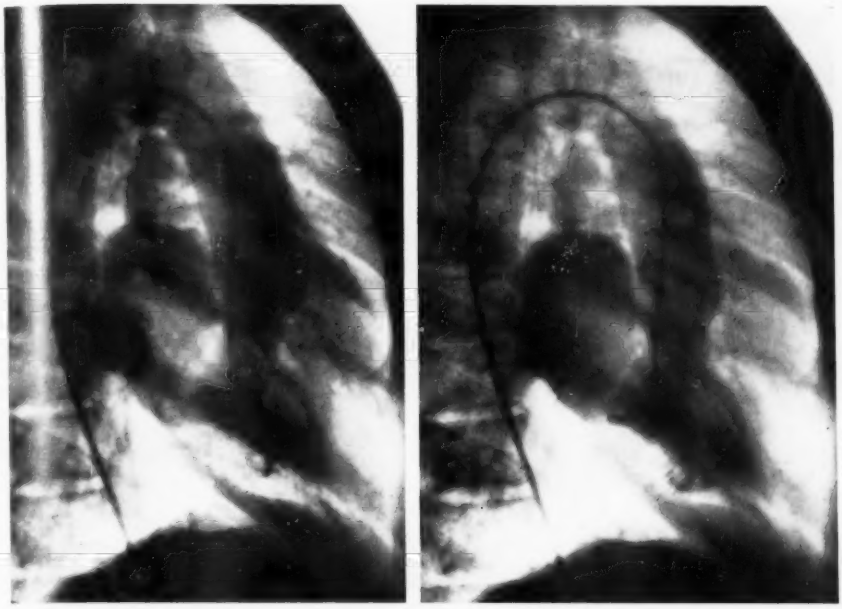

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Fig. 1. Left cardiac ventriculography in mitral insufficiency. a) Systole. Definite regurgitation into the left atrial chamber. b) Subsequent diastolic phase. Persistent and increased opacity of the left atrium. No significant variation in volume of the left atrium is noticed between the two phases. Surgical exploration proved the presence of obvious endo-atrial reflux.

Results

We have used left cardiac ventriculography through percutaneous catheterization of the femoral artery as a routine preoperative method in over 20 cases of mitral disease. More than half of these had pure mitral stenosis without any degree of regurgitation into the left atrium. The findings were confirmed at operation. Different degrees of atrial regurgitation were noted in the remaining cases (see Fig. 1); in 5 of them surgical exploration permitted the amount of mitral regurgitation to be checked.

GILMAN et coll. tried to establish a connection between the degree of regurgitation into the left atrium, as measured roentgenologically, and the surgical evaluation of the degree of mitral insufficiency. In 17 out of 28 cases showing angiocardiographic evidence of mitral insufficiency, they found almost complete agreement. In the remaining 11 cases, the evaluation be-

tween the angiocardiographic and surgical data showed slight variations, but in almost all cases the presence and amount of the reflux was significant due to indisputable mitral valve insufficiency.

As SMITH et coll. have pointed out, attention must certainly be paid to the size of the left atrial chamber in the grading of patients presenting evidence of regurgitation into the left atrium; in other words, the degree of regurgitant filling of the left atrium is likely to vary with the volume of the latter, given the same degree of actual leak through the mitral valve (GILMAN et coll.).

On the other hand, as GILMAN et coll. have stressed, the small disparities between the roentgenologic evaluation of the degree of mitral insufficiency and the surgical control are not surprising in that variations in stroke volume, pulse rate, cardiac output, blood pressure and production of arrhythmias which may occur in both cases are factors that must be taken into account in the determination of these disparities.

Conclusions

A comparison of the roentgenologic data with the results of the surgical examination of the mitral valve has shown, in a considerable number of cases, that mitral insufficiency may within certain limits be precisely established, even as to amount, by means of the injection of a contrast medium into the left ventricle.

It appears from a comparison with other procedures that left cardiac ventriculography after percutaneous catheterization of a femoral artery is the most simple one to perform and is practically free from risks and counter-indications. Serial films for a sufficiently long period must be obtained so as to show the contrast medium while it persists in the left ventricle and thus record the behaviour of the reflux in more than one heart cycle. This is to avoid the possibility of transitory mitral regurgitations (STAUFFER et coll., DALLA ROSA et coll.), which admittedly may occur and lead to errors in diagnosis. For the same reason simultaneous electrocardiographic control is advisable for the recording of disturbances in rhythm.

Left cardiac ventriculography may also constitute an efficient procedure for the evaluation of the result of the surgical correction of mitral insufficiency.

SUMMARY

Left cardiac ventriculography by means of retrograde percutaneous catheterization of a femoral artery appears to be an accurate method for the pre-operative assessment of the presence and degree, or absence, of mitral regurgitation. The results in a material of 20 cases are reported. Any significant degree of regurgitation into the left atrium during the procedure is considered pathognomonic of mitral valve insufficiency.

ZUSAMMENFASSUNG

Linksseitige Herz-Ventrikulographie mittels retrograder perkutaner Katheterisierung der Femoralarterie scheint eine genaue Methode zur präoperativen Bestimmung des Vorliegens bzw. Ausdehnung, oder Fehlens von mitraler Regurgitation zu sein. Die Ergebnisse eines Materials von 20 Fällen werden berichtet. Ein signifikanter Grad von Regurgitation in das linke Atrium wird als pathognomonisch für Mitralklappeninsuffizienz angesehen.

RÉSUMÉ

L'examen radiographique du ventricule gauche du coeur par cathétérisation rétrograde percutanée d'une artère fémorale semble être une méthode précise pour apprécier avant l'opération la présence et le degré, ou l'absence de régurgitation mitrale. Les auteurs présentent leurs résultats sur 20 cas. Toute régurgitation importante dans l'oreillette gauche au cours de cet examen est considérée comme pathognomonique d'une insuffisance de la valvule mitrale.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: T. ROSENDAL), AND THE EAR, NOSE AND THROAT DEPARTMENT (DIRECTOR: O. METZ), SUNDBY HOSPITAL, COPENHAGEN, DENMARK

VALUE OF DIFFERENT PROJECTIONS IN DIAGNOSING CHOLESTEATOMA

by

GERT JENSEN, CHR. JESPERSEN and S. BRÜNNER

American and Scandinavian authors are not agreed regarding the value of the various projections in demonstrating bone destruction of the antrum or attic in cases of chronic middle ear infection. For instance, MACMILLAN (1932) found bone destruction of the temporal bones in 45 per cent of 288 cases of surgically confirmed cholesteatoma with Law's projection and in 60 per cent of cases when using Towne's projection, whereas HOLMES (1938) and CHIAT & KITTREDGE (1958) noted destruction in 50 per cent of cases when the same projections were employed. A higher percentage has been reported in the Scandinavian literature. Using Runström's projections WINDEREN & ZIMMER (1954) reported signs of cholesteatoma in 75 per cent of 131 surgically verified cases.

The projections used in the above-mentioned studies (LAW's, TOWNE's, and RUNSTRÖM's) have been developed from the Schüller and Stenvers' views of the temporal bones. Common to all these projections is the difficulty of avoiding superimposition of the antrum and attic on the dense bone around the semicircular canals and cochlea. Chaussé's projection III (1950) afforded improved possibilities of showing the antrum and attic thrown free from the labyrinth

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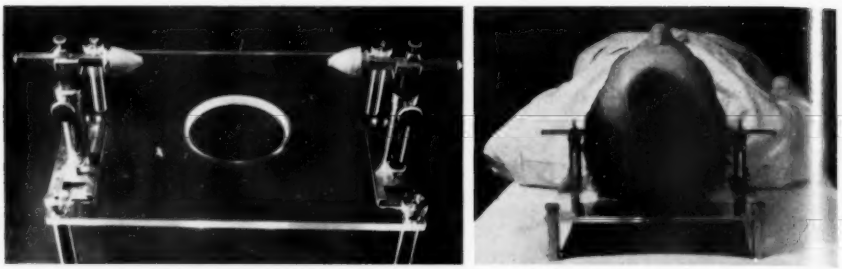

Fig. 1. Apparatus or placing the temporal bones in the same horizontal plane (after ROSENDAL 19 3).

and of demonstrating the lateral wall of the attic and the superior wall of the external auditory meatus.

Examples of Chaussé's projection III in diagnosing bone destruction caused by cholesteatoma in the antrum or attic have been published by ROSENDAL & EWERTSEN (1952) who also described the roentgenologic anatomy of the antrum, attic, and the superior wall of the external auditory meatus. The value of Chaussé's projection III based upon a large series of surgically confirmed cases has not previously been assessed and compared with the other usual projections.

Tomography of the temporal bones in the anteroposterior view has afforded a possibility of further improving the demonstration of the antrum and attic, as well as their bony limits. By this method TARP (1959) demonstrated bone destruction in 19 out of 22 confirmed cases of cholesteatoma, i. e. in 82 per cent, whereas the usual projections afforded a means of diagnosis in 53 per cent of cases.

The present authors investigated the relative values of the various projections. All their cases of chronic otitis media were examined with the Schüller projection and with the Runström III projection and, after 1950, with the Chaussé III projection as well. Some of the cases were also examined with Mayer's projection. In the event of any suggestion of a fistula of the labyrinth ROSENDAL & EWERTSEN's transorbital projection (1952) was used.

Since 1956 linear tomography has also been employed. The patient lies supine, his head firmly held by two rods in a special fixation apparatus (Fig. 1) to project the lateral ends of the external auditory meatuses in the same horizontal plane.

A primary diaphragm with a slit-shaped opening is used, producing a field measuring 18 × 5 cm. The distance between the sections is 3 mm. By this technique both temporal bones are shown symmetrically so that the two sides may be compared.

Material

The material comprises 80 patients (Table 1), 31 females and 49 males, operated upon during the period 1950—1958 for chronic otitis media and in which operation revealed bone destruction. The majority (62) were over 20 years of age, and 10 were children ranging in age from 6 to 10 years. At operation it was found that in 41 cases the cholesteatoma was located in the antrum, in cases in the attic, and in the remaining 36 in both the antrum and attic. The operations also revealed a fistula running into the lateral semicircular canal in 6 instances. In 4 cases the destruction was so widespread that the dura mater overlying the tegmen was exposed. The reports do not give the precise measurements of the cavities, 50 being described as the size of 'hazel nuts' or

Table 1

Presentation of material and results of studies with different projections

Operative findings Site of cholesteatoma	Number	Projection			Total
		Schüller	Runström III	Chaussé III	
Antrum	41	14	11	22	26
Antrum + attic	36	18	10	26	28
Attic	3			2	2
Total	80	32 = 40 %	21 = 26.25 %	50 = 62.5 %	56 = 70 %
Complications					
Fistula of labyrinth	6			1	
Denuded dura	4				
Size of bone destruction					
Hazel nut and greater	50	26	17	39	
Pea	3	1	2	3	
Dilated antrum and attic	27	5	2	8	

Table 2

Forty cases of destruction of the superior wall of the external auditory meatus shown in the Chaussé III projection

Operative findings	Number of cases
Destruction in attic	28
Destruction in antrum only	12
Otoscopic findings	⊖
Defect of pars flaccida	23
No characteristic findings	10
Peripheral defect of pars tensa	7

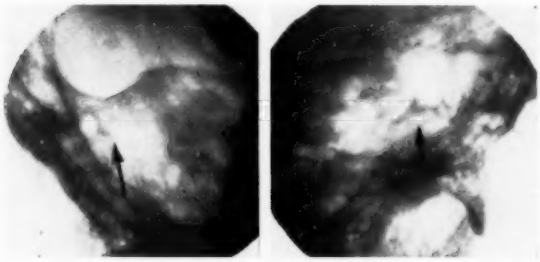

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Fig. 2. a) Right temporal bone, Chaussé's projection. Destruction of medial third of superior wall of external auditory meatus (arrow). b) Unaffected left bone for comparison, showing normal superior wall of external auditory meatus (arrow).

'nut kernels', 3 as the size of 'peas', while in 27 the reports merely mention dilatation of the antrum or attic. The condition of the superior wall of the external meatus is not stated.

All the patients were examined with the Schüller, the Runström III, and Chaussé III projections, and bone destruction was diagnosed if there was evidence of it in only one of these projections, viz. in 70 per cent of the cases. It is apparent from Table 1 that Chaussé's projection contributed most to the diagnosis, viz. in 62.5 per cent of the cases while bone destruction was noted with Schüller's projection in 40 per cent, and with the Runström III projection in 26.3 per cent of the cases. Mayer's projection is not included in the table, since it was not used systematically. Out of the 56 cases where it was used, it afforded evidence of bone destruction in 25 per cent. From the bottom section of the table it may be seen that the cavity must have reached a certain size in order to be demonstrable in the roentgenogram.

Table 2 shows the relationship between absence of the superior wall of the external auditory meatus in the Chaussé III projection and the operative findings and otoscopic appearances, respectively. In the 40 cases where the Chaussé III projection revealed absence of the superior wall of the external auditory meatus, operation disclosed destruction in the attic in 28 and destruction in the antrum in only 12 cases. In other words, the majority of cases showed agreement between the roentgen findings with the Chaussé III projection and the site of the lesion in the attic. In the 12 cases with cavities in the antrum, the absence of the superior wall of the external auditory meatus might have been due to decalcification. As already mentioned, the operative reports do not mention the condition of the superior wall of the external auditory meatus, and it cannot be ruled out that it may have been destroyed in some of these 12 cases.

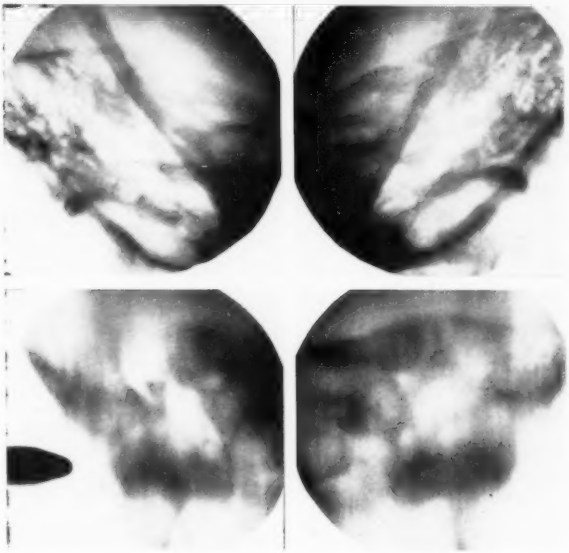

Fig. 3. Upper views. Right and left ear, Chaussé III projection. Cellular structure masking superior wall of external auditory meatus which is barely discernible on the right and is not seen on the left side. Lower views: Tomograms a. p. of right and left temporal bones; left destruction of superior wall of external auditory meatus and of lateral wall of attic; ossicles absent; right normal superior wall and ossicles.

Comparing the findings noted with the Chaussé III projection with the otoscopic appearances, it was found that 23 cases had defects of the pars flaccida, while in 10 cases the otoscopic appearances could not be definitely assessed. In the remaining 7 cases there was a question of peripheral defects of the pars tensa. At the time of operation, the lesion had spread to the attic in 5 of the 7 cases.

Six patients were found to have a fistula of the labyrinth at operation. This had been indicated by the Chaussé III projection in only one case, whereas the transorbital projection of Rosendal had shown fistula formation in 3 cases. The explanation is probably that the Chaussé III projection shows the central part of the lateral semicircular canal, whereas the Rosendal projection gives a tangential view of its anterior aspect, the most common site of fistulae.

The following 4 cases serve to show the value of the Chaussé III projection in the roentgen examination of patients with chronic otitis media in demonstrating bone destruction.

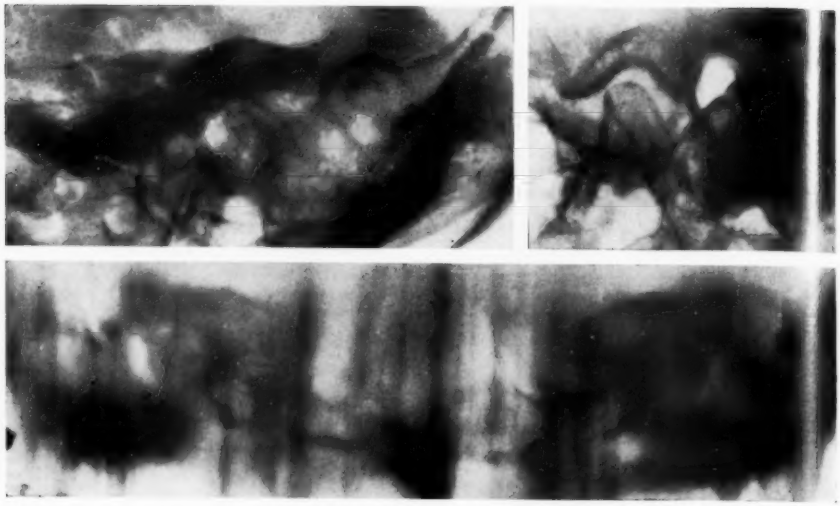

Fig. 4. Upper left: Runström III projection, hazel-nut-sized cavity at the site of antrum. Upper right: The same ear, Schüller's projection. Lower views: Tomograms of right and left ears. Hazel-nut-sized cavity at the site of left antrum. Superior wall of external auditory meatus absent. No abnormalities on right side.

Case reports

Case 1. Female, aged 60, with a history of periodical discharge from the right ear and impaired hearing from childhood. Otoscopy revealed a fistula in the epitympanic recess. Chaussé III (Fig. 2): On the right side widespread destruction. The superior wall of the external auditory meatus and the lateral wall of the attic are absent. No abnormalities on the left side. Operation revealed a hazel-nut-sized cavity with cholesteatoma in the antrum and attic.

Case 2. Boy, aged 6 years. During the 4 months preceding admission: discharge from the left ear. Otoscopy revealed an irregular defect beneath the posterior fold of the malleus. Chaussé III (Fig. 3) showed how preserved cellular structure may hide the superior wall of the external auditory meatus. The tomograms showed a normal superior meatal wall on the right as indicated by the arrow. On the left side, the superior wall of the external auditory meatus is absent medially, and in the tympanic cavity the ossicles are absent. Operation revealed necrotic osteitis of the entire mastoid process, encroaching upon the middle ear. The incus was totally destroyed.

Case 3. Male, aged 54, with a history of chronic otitis for the previous 15 years. Otoscopy revealed a large posterior marginal defect, extending to the tympanic cavity. In the Runström III projection the roentgenograms (Fig. 4) showed superiorly on the left a hazel-nut-sized cavity at the site of the antrum. On the right side there was also a cavity at the site of the antrum in Schüller's projection. At the bottom, the tomogram showed normal conditions on the right side. On the left side, a cavity, as large as a hazel-nut, lay at the site of the antrum, and the

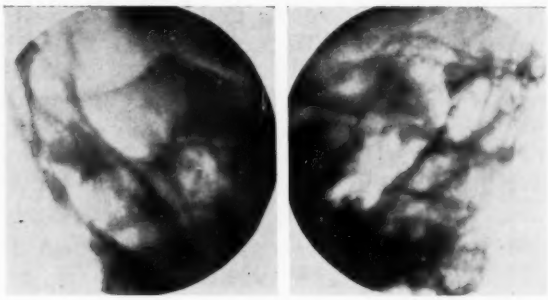

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Fig. 5. a) Right ear Chaussé III projection. Cavity the size of a hazel-nut at site of antrum. Destruction of the upper part of the lateral wall of the attic. Superior wall of external auditory meatus preserved. b) Normal left ear.

superior wall of the external auditory meatus was absent. Operation revealed a hazel-nut-sized cholesteatoma in the antrum and destruction of the ossicles.

Case 4. Male, aged 31, with a history of discharge from the right ear since childhood. Otoscopy revealed a cushion of granulation tissue covering the posterosuperior portion of the pars tensa. Chaussé III (Fig. 5): Normal conditions on the left side. On the right side, a cavity, larger than a hazel-nut, at the site of the antrum, extended to the superior portion of the lateral wall of the attic cavity, but the tip of the superior wall of the external auditory meatus was preserved. Operation revealed a spontaneous cavity at the site of the antrum and attic.

Table 3

Comparison of ordinary roentgenography and tomography of the temporal bones in 21 cases

Operative findings Site of cholesteatoma	Number	Demonstrated by:			Tomography
		Schüller	Runström III	Chaussé III	
Antrum	7	3	3	5	4
Attic	13	7	4	9	12
Antrum + Attic	1			1	1
Total	21	10 = 47.6 %	7 = 33.3 %	15 = 71.4 %	17 = 80.9 %
Complications					
Fistula of labyrinth	2				2
Site of bone destruction					
Hazel-nut	13	9	5	11	13
Pe	2	1	2	2	2
D ted antrum and attic	6			2	3

Table 3 sets out the result of tomographic studies of the temporal bones, compared with the 3 projections. The cases in which the different projections showed destruction are listed under each projection separately and are for practical reasons calculated as percentages. By means of the current methods, the diagnosis was made in 16 out of the 21 cases, or in 76.2 per cent. As evident from the table the Chaussé III projection contributed more towards diagnosing bone destruction than did the Schüller and Runström III projections. The tomographic examination increased the chances of diagnosing bone destruction up to 80.9 per cent.

SUMMARY

The relative value of the Schüller, Runström III, and Chaussé III projections in the demonstration of bone destruction in chronic otitis media, in a material of 80 cases, is discussed. Destruction could be shown in about 62 per cent of cases by means of the Chaussé III projection, a figure which was increased to about 80 per cent by tomography.

ZUSAMMENFASSUNG

Der relative Wert der Projektionen nach Schüller, Runström III, und Chaussé III zur Demonstration von Knochendestruktionen bei chronischer Otitis media wurde an Hand eines Materials von 80 Fällen besprochen. Mittels der Chaussé III Projektion konnten in ca 62 % der Fälle Destruktionen nachgewiesen werden. Diese Zahl wurde mit der Tomographie auf ca 80 % erhöht.

RÉSUMÉ

Les auteurs ont comparé sur 80 cas la valeur relative des incidences de Schüller, de Runström III et de Chaussé III pour mettre en évidence la destruction osseuse dans l'otite chronique moyenne. L'incidence de Chaussé III a permis de mettre en évidence une destruction dans environ 62 % des cas; ce nombre atteint environ 80 % quand on utilise la tomographie.

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR: L. L. ROBBINS), MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS, U.S.A.

TWO VASCULAR GROOVES OF THE EXTERNAL TABLE OF THE SKULL WHICH SIMULATE FRACTURES

by

HERBERT SCHUNK and YOSH MARUYAMA

The present investigation has been conducted with reference to two grooves of the skull commonly mistaken for fractures. One of these is observed on the lateral projection in the temporo-parietal region and the other in the frontal region. Their recognition and proper interpretation is important since it may spare the patient inconveniences and possibly make a neurosurgical intervention unnecessary.

The aim of investigation has been threefold: first, to study dried skull specimens from the Warren and Peabody Museums of the Harvard Medical School and roentgenograms of selected specimens (a total of 556 skulls were reviewed), secondly, to undertake anatomical dissections of cadaver specimens, and lastly, to correlate with clinical skull roentgenograms. A total of 2 306 skull examinations, performed at the Massachusetts General Hospital during the period July 1, 1958, to June 30, 1959, were reviewed.

Results

The temporo-parietal region. On the external table of the skull, in the temporo-parietal region, a linear groove was observed in 72 % of the specimens as seen in the Table. This grooving was bilateral in 41.5 % of the specimens,

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Table

Groove observed in dried skull specimens examined (a total of 556)

	Middle temporal groove		Supraorbital groove	
T al with grooving	72 %	401	27 %	152
U lateral	30.5 %	169	15.5 %	87
Bi teral	41.5 %	232	11.5 %	65
Bi teral in positive specimens	58 %		43 %	
V y deep	2 %	10	3 %	17
Br ching	45 %		24 %	
Av rage angle of inclination	95°—100°			

i. . 58 % of those showing the groove. This originated above the external auditory meatus, near the zygomatic-temporal junction, and extended vertically or semivertically over the squamosal portion of the temporal bone.

The groove showed different features depending on the portion studied. The first third of the groove may show a slight bend in its lowermost portion with either a convexity pointing posteriorly, a minimal anterior bowing, or a straight linear course (Fig. 1). Forty-five percent of the skulls showed branching of the groove into anterior or posterior branches (Fig. 2). The middle third of the groove lay invariably in the posterior half of the temporal squama, being quite linear and extending vertically or obliquely over the squama, and sometimes crossing the temporal suture into the parietal bone. In a single instance, a rather deep impression was noted, arising above the temporal suture and extending onto the parietal bone without an external impression in the temporal region. The outer third of this groove, beyond the temporal suture, became indistinct and had a variable course.

It was noted that the majority of these grooves were shallow, and usually broad, and could not in the roentgenogram be confused with a fracture. An impression sufficiently deep to appear as a line on roentgenograms was found in 2 % of the dried skulls, (Fig. 3). This correlated well with our clinical material. No examples of very deep bilateral grooves were observed in our specimens.

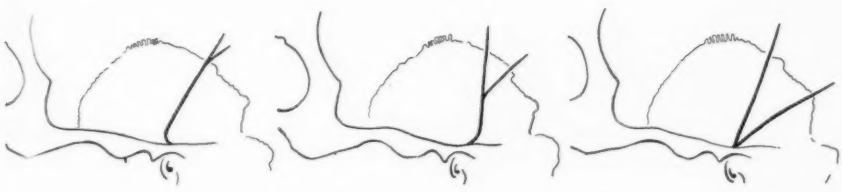


Fig. 1. Variations in the course and branching of the groove of the middle temporal artery. a) An anterior bow inferiorly, unbranched squamosal course and parietal branching. b) Posterior bow inferiorly with branching in the mid-portion of the squamosal bone. c) The course is linear with branching near the zygomatic arch.

Fig. 2. Dried skull specimen showing an anatomically possible variation. Anterior and posterior branches can be seen, and the course in the parietal region is demonstrated.

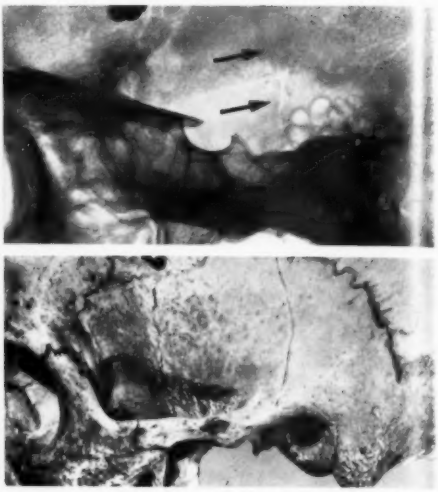


Fig. 3. Dried skull specimen and corresponding roentgenogram. Groove corresponding to one seen on the external table of the skull. Angle of inclination 95°, which is in the average range noted for a mesocephalic skull. In the roentgenogram the groove is clearly outlined by contrast medium.

Twenty-seven of 2 806 skulls or approximately 1 % of the clinical roentgenograms reviewed showed distinct lines in this region of sufficient clarity to be misinterpreted as fractures; however, faint grooves were seen more frequently. The clinical radiographic features are as follows: The line originates in a triangle formed by the anterior clinoid-Basion-Citelli angle. The variations of the lower course of the groove were similar as in our anatomical series, i. e. the course may be straight, may show a slight convex posterior curve, or a slight anterior convex curve. If the sphenoid sinus is well pneumatized, the lower portion may be recognized. The study of this lowermost portion is most important, as the previously described curvature of the groove in this region can often be demonstrated by slightly oblique lateral projections. Branching was rarely noted in the lower third of the vascular groove. The course in the squamous portion of the temporal bone is linear and straight and intersects the grooves of the middle meningeal vessels on the table of the skull. This latter can be distinguished by excellent quality stereoscopic films which will reveal these vessels to lie in a slightly different plane. However, thinness of the temporal squama (usually less than 0.5 cm) makes adequate examinations extremely difficult. The different courses of the middle meningeal and the middle temporal arterial grooves are illustrated in Fig. 4.

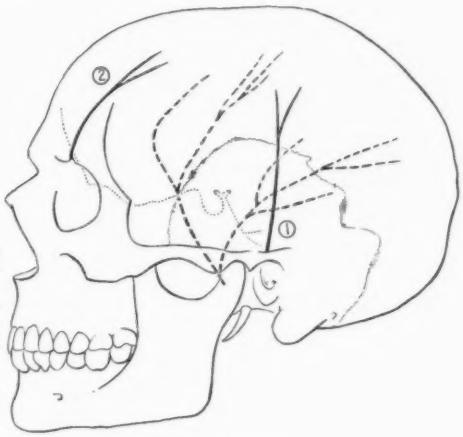
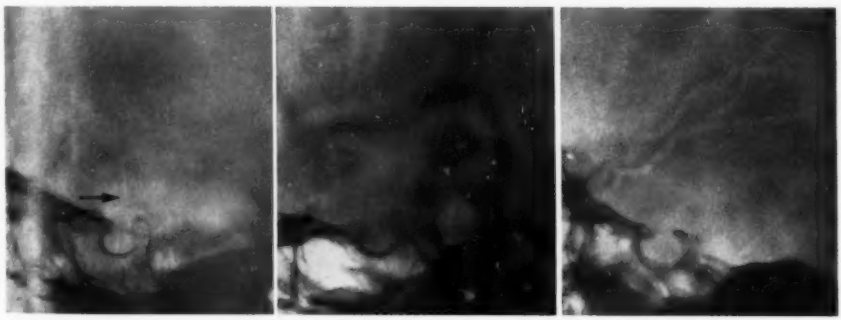


Fig. 4. Diagram of the inner and outer table of the skull. The grooves of the middle meningeal artery in contrast to those of the (1) middle temporal group are much more abundant and run in a more oblique course; (2) the supraorbital artery groove is also shown.

Middle meningeal artery and branches ----
Middle temporal artery ① ————
Supraorbital artery ② ————

Certain general observations regarding the degree of angulation of the groove were noted both on specimens and clinical roentgenograms. This angle was obtained by connecting the base line from the lower orbital wall to the external auditory meatus with the groove, and at the point of intersection measuring the angle from the anterior margin. In the mesocephalic skull, the angle of inclination usually lies between 95 to 100°. In the brachycephalic skull the line tends to be more vertical, and in the dolichocephalic skull the angle is apt to be greater, often being over 125° (Fig. 5). These lines lack the distinctness of true recent fractures in this region, and on close observation



a b c

Fig. 5. Three anatomical variations of the middle temporal artery groove as seen on routine clinical skull roentgenograms. The brachycephalic skull tends to have the vertical grooves (a); the usual groove is the one demonstrated in the mesocephalic skull (b); the dolichocephalic skull tends to have the greater angle of declination (c).

Fig. 6. A true linear racture in the temporo-parietal region. The margins are distinct in contrast to the middle temporal artery grooves which do not pass completely through the table of the skull.

Fig. 7. Post-mortem anatomical dissection. The middle temporal artery on the external table of the skull runs in a characteristic linear course; it lies deep at the temporalis muscle (retracted), and branching is seen.

will be noted to pass incompletely through the external table of the skull (Fig. 6). The line is not visible in the antero-posterior plane. If the line is bilateral, it should follow similar courses on both sides. This also represents a distinguishing feature which can be evaluated on the oblique and stereoscopic films.

In five anatomical dissections, a small artery was found to groove the external table of the skull underlying the temporalis muscle (Fig. 7). Its course is linear and corresponds to that observed in our other studies. This vessel is the middle temporal artery and was proved by perfusion to be a branch of the external carotid artery. The groove thus represents a vascular impression caused by the middle temporal artery.

The supraorbital region. The second vascular groove on the external table of the skull, which also can simulate a fracture line, occurs in the frontal region and again can follow a quite linear course. It was observed less commonly, being seen in 27 % of the dried skull specimens (see Table). This line is bilateral in 11.5 % of the specimens, i. e. 43 % of those showing the groove, and was again, in the great majority of cases, quite shallow and broad. A much greater variability of all its features was observed. The vascular groove exhibited not only variations in length but also in depth. It could be single (Fig. 8) but frequently multiple, parallel or branched; grooves were noted. This latter finding was evident on 24 % of the specimens showing

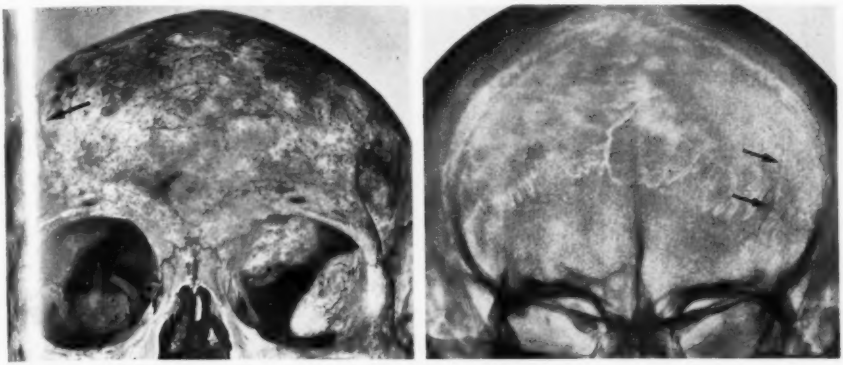


Fig. 8. The supraorbital groove in a.p. projection. Its course is vertical but slightly arched laterally toward the region of the coronal suture. Inferiorly, the supraorbital foramen can be seen. The roentgenogram of the skull reveals a groove corresponding to this region.

grooving. The groove has its origin near the supraorbital foramen, though it could occur in the frontal bone as a deep groove in practically any relationship to the foramen and orbital ridge, i. e. just adjacent to, or on 2 to 3 cm distance from it (Fig. 9). These grooves extend posteriorly and upward in an oblique fashion toward the coronal suture in the lateral projection. In p.a. films, as illustrated in Fig. 8, the groove begins in the region of the mid-orbital ridge, and ascends almost vertically, but angulates and arches slightly laterally toward the region of the coronal suture. Deep grooves were noted in 3 %

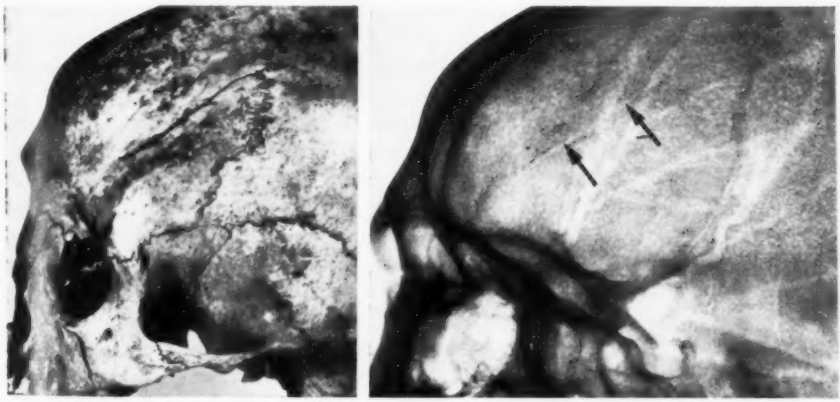


Fig. 9. The supraorbital groove in lateral projection, showing its course toward the coronal suture superiorly and the supraorbital foramen inferiorly. The roentgenogram shows a groove corresponding to this region.

Fig. 10. Roentgenogram showing the supraorbital groove, as seen on lateral projections in clinical skull examinations.

Fig. 11. Anatomical preparation of the frontal bone after retraction of the scalp which is reflected over the orbital ridges. The groove is the vascular impression of the supraorbital artery.

of dried specimens, but as not all of them were sufficiently linear and unbranched in course they could not be mistaken for fracture lines.

Ten of 2 806 clinical skull roentgenograms, or less than 1 %, revealed lines of sufficient clarity and distinctness to cause concern about a fracture in this region (Fig. 10). However, faint grooves were seen much more frequently. This is explained by the broader, flatter nature of these grooves; there are frequently multiple parallel grooves and branching. When the grooves are bilateral, this may help to distinguish them from fractures, as their course is usually symmetrical on both sides of the skull (Fig. 12). Various radiographic features are demonstrated and may be compared with the anatomical specimen seen in Fig. 11. The groove is the vascular impression caused by the supraorbital artery.

Discussion

The middle temporal artery groove has been observed and commented upon by only a few investigators. DYKE and CHILDE believe it to be a branch of the middle meningeal artery and have described many of the features that we have been able to confirm by our studies. LINDGREN has demonstrated the appearances of the groove and pointed out that they may simulate frac-

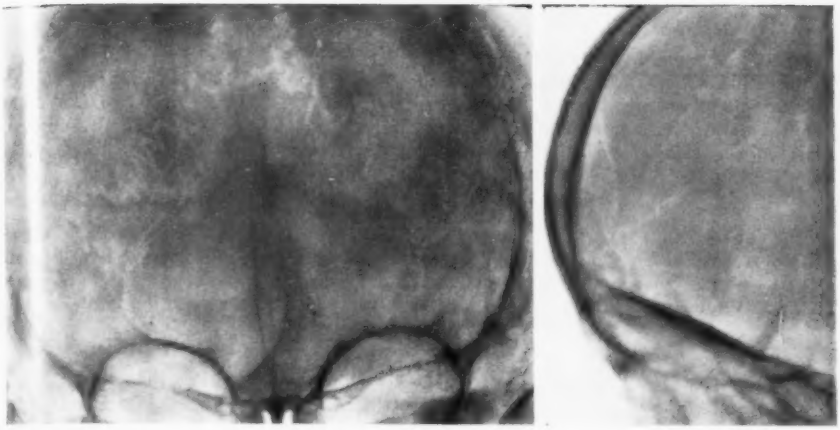


Fig. 12. Roentgenograms from a 7-year-old child. Fracture was suspected. Bilateral supraorbital grooves and 'stellate' branching are evident in the p.a. projection.

tures. ETTER mentions it as an aberrant vascular groove, and in his text has an illustration of the same groove. An anatomical study is reported by STIBBE and SPALTEHOLZ. Our investigations localize this groove to the external table of the skull and to a specific anatomic structure. Our findings indicate that this represents a common anatomical variation of a normal structure that can on occasion be of sufficient magnitude to be of concern to radiologists and clinicians. The importance of recognizing it as a vascular groove is emphasized, as many of its features are compatible with those frequently described for linear skull fractures, and hence incorrectly interpreted.

The middle temporal artery grooves the external table of the skull in the temporo-parietal region. We have correlated the anatomical features of the artery and groove with the clinical roentgenographic features. Familiarity with this line, its position and location, and anatomical variations is of greatest importance.

The roentgenographic appearance of the vascular groove of the external table of the skull, situated in the frontal region and due to the supraorbital artery, is also reported and discussed. It is apparent that familiarity with the usual position, location and anatomical features of this groove will serve to distinguish it from a linear fracture in these regions. The radiographic findings again closely parallel the anatomically observed findings. In addition to the knowledge of its usual location, features such as branching, multiple parallel grooves, the occasional bilaterality, all of which point to the mid-supraorbital region, serve to distinguish it from a true fracture.

Acknowledgements

We would like to acknowledge our obligation to Dr. Paul I. Yakovlev, Clinical Professor of Neuropathology and Curator of the Warren Anatomical Museum, and to Dr. William White Howells, Curator of Somatology and Professor of Anthropology, Peabody Museum, Harvard University, for making available to us the skull specimens used in this study.

SUMMARY

Two grooves of the skull which are frequently mistaken for fractures have been demonstrated to be vascular grooves of the external table of the skull, due to the middle temporal artery in the temporo-parietal region, and to the supraorbital artery in the frontal region.

ZUSAMMENFASSUNG

Es wurde gezeigt, dass zwei linienförmige Strukturen am Schädel, die häufig mit Frakturen verwechselt werden, Gefässfurchen darstellen, die der Art. temp. media in der temporo-parietalen und der Art. supraorbitalis in der Frontalregion zugehören.

RÉSUMÉ

Les auteurs ont montré que deux sillons linéaires du crâne qui sont fréquemment pris par erreur pour des fractures sont des sillons vasculaires de la table externe du crâne, dus à l'artère temporale moyenne dans la région temporo-pariétale et à l'artère sus-orbitaire dans la région frontale.

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR: JOHN H. GILMORE)
OF ILLINOIS MASONIC HOSPITAL ASSOCIATION, CHICAGO, U.S.A.

OSSIFYING PNEUMONITIS AND CALCINOSIS

Report of a case

by

CONSTANTINE SOTER, Y. BERKMEN, H. GÜR, A. A. HADZIDAKIS and JOHN H. GILMORE

The formation of bone in the lungs is unusual, and the association with massive calcinosis is a very interesting and rare phenomenon. The case now presented has shown so many unusual features that we believe it worthy of publication.

A male, aged 50, was admitted to I. M. H. in December 1954, with complaints of cough, fever and pleuritic pain in the left chest. The clinical picture was that of a virus pneumonitis. The lungs at roentgen examination were essentially clear, with slight amount of pulmonary fibrosis, and slight cardiac enlargement (Fig. 1). Past history revealed that the man had been in poor health for a long time, and had several times had fever and jaundice; no satisfactory response to antibiotics. Tests for psittacosis gave positive high titer. At this time, liver and kidney pathology was also observed. The patient was discharged with a persistent low grade fever.

In December 1955 the patient showed increasing dyspnea with a history and findings consistent with pneumonia. In January 1956 he was found to be anemic, and with these complaints was admitted to another hospital, where the following laboratory tests were made. The blood pressure of the patient had been around 160/88. W. B. C. of 11 000 had been increased several times, R. B. C. of 4.1 million, Hg 55 %, sedimentation rate 55 mm. The

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Fig. 1. Slight amount of fibrosis in the lungs. The heart is slightly enlarged.

pulmonary function test had shown moderate to severe reduction of ventilation. Vital capacity and maximum breathing capacity were severely reduced. Tuberculin tests as well as histoplasmin and blastomycosis tests were negative. Bone marrow study had shown granulocytic hyperplasia and thrombocytosis, liver biopsy portal cirrhosis with fatty change focally, and anterior scalene node biopsy had shown reticulo-endothelial hyperplasia and hemosiderin deposition. Subcutaneous renal biopsy had revealed nephrocalcinosis with evidence of chronic tubular obstruction and hemosiderosis in Henle's tubules. No significant glomerular, vascular or inflammatory process was seen. Skin and muscle biopsy had shown mildly and irregularly atrophic skeletal muscle. No evidence of angiitis or myositis was observed.

Several examinations of the serum calcium were found to be in a range between 13.9 and 9.2, and the phosphorus between 7 and 3.8.

On May 9, 1956, a roentgen examination of the chest was reported negative. On June 6, 1956, an examination of the chest showed bilateral parenchymal lesions extending from apices to base and consisting of irregularly disseminated, patchy and nodular masses; these had increased in size and extent at an examination in July. The areas then appeared considerably larger and slightly confluent. There was a moderate amount of hilar lymphadenopathy.

The patient returned to our hospital in November 1958 with complaints of dyspnea, weakness, etc. The chest roentgenogram at this time (Fig. 2) showed multiple nodular densities in both lung fields, confluent in the mid lung areas, with evidence of several calcification like densities in the center of the nodular lesions, diffuse fibrosis and a moderate amount of emphysema. The left ventricle of the heart was prominent and hypertrophic, and the aorta was wide and tortuous.

The patient's final admission to I. M. H. was in February 1959; he then expired having marked dyspnea, cyanosis and progressive right heart failure.

Fig. 2. Multiple nodular densities partly confluencing, partly calcified.

Pertinent autopsy findings

Lungs. The right lung, which retained its usual shape, weighed 650 g. The external surface was extensively covered with dense fibrous adhesions. The interlobar fissures were obliterated. Multiple firm but diffusely scattered nodules, measuring from 0.5 to 2.0 cm in diameter, were palpable, and in certain areas formed confluent, firm masses of irregular shape and size. The nodular lesions were mainly palpable in the upper portion of the lung, decreasing toward the base. The hilar lymph nodes were enlarged, measuring up to 3 cm in diameter. They were discrete, soft, succulent and moderately anthracotic. On cross section, the cut surface was slightly bulging with diffuse grey areas. The bronchi were of average caliber with pink lining. The lung cut with remarkably increased resistance and gave a gritty sensation. The nodular lesions were distinct from the surrounding parenchyma, and the surface of the lesions resembled fine sand. The blood vessels were of normal caliber and consistency. The left lung weighed 810 g, with similar findings as described in the right.

Roentgenograms of the lungs and heart after the resection in toto (Fig. 3) and after section of the right lung (Fig. 4) showed very well the findings described.

Heart. The right ventricle was 0.5 cm thick and slightly dilated. The left ventricle was moderately dilated and the wall measured 1.8 cm. The left atrium was slightly dilated, and the mitral ring was markedly calcified. The coronary arteries showed considerable arteriosclerotic changes with stenosis of the lumen and almost complete occlusion of the circumflex branch of 1 cm in length.

Kidneys. Each kidney weighed 200 g. Both kidneys cut with average resistance. The parenchyma was of average thickness.

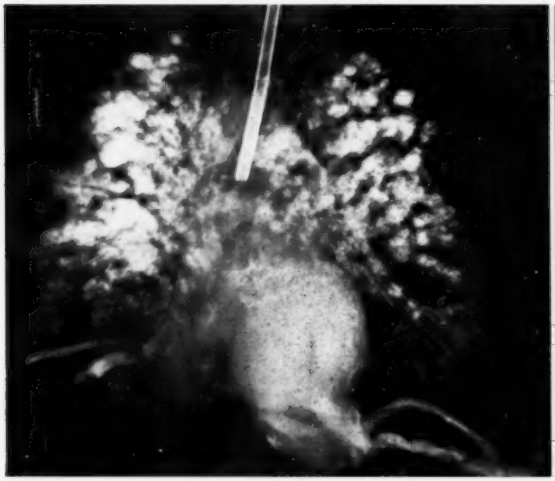

Fig. 3. Roentgenogram of heart and lungs with mild insufflation immediately after resection showing degree of calcification.

Fig. 4. The distribution of the lesions in a section of the right lung.

Microscopic findings

Lungs. There was a large amount of calcification, involving the alveolar walls. In the areas of minimal change, the alveolar septum was preserved, and there was slight deposition of calcium granules apparently in the capillary walls. In more advanced stages the alveolar spaces were filled with material which appeared to be partly fibrous, but, in large parts, calcified and amorphous. There were smaller zones of other types of change: atelectasis in alveloar spaces, mononuclear exudate and organizing adenous material with marked proliferation of the septal surface and fibrous thickening of many alveolar walls without calcification. There was some increase in lymphocytes. The small and large bulges of the pulmonary arteries showed only moderate calcification deposits. Some of the small bronchi revealed calcification deposits in the submucosa.

Stomach. The lamina propria showed extensive calcified masses obliterating the glands but they generally appeared confined to the connective tissue.

Kidneys. Extensive calcification involved the interstitial tissues, finally involving and destroying a few tubules. Focal aggregates of mononuclear cells were present. The glomeruli and tubules were otherwise well preserved.

Bone marrow. The bone marrow was hyperplastic involving both the red and white cell elements.

Parathyroids. Only two parathyroids, of average size and with moderate fat invasion were recovered. The parenchymal cells were mostly of chief-cell type with some clear water cells.

The *pathologic diagnoses* were as follows: Massive calcinosis of the lungs with fibrosis; extensive calcification of arteries; calcification deposits in gastric mucosa; generalized arteriosclerosis, moderate; arteriosclerosis of coronary arteries, severe; old infarcts of heart; myocardial hypertrophy; chronic passive congestion of lungs; recent infarct of spleen; cirrhosis of liver (? Laennec type); splenomegaly; hyperplasia of bone marrow; hyperplasia of lymph nodes. Subsidiary diagnoses: Fibrous pleural adhesions; focal pulmonary atelectasis.

Doctor A. Liebow made the additional remark: "The findings of the pulmonary biopsy appeared analogous to 'ossifying pneumonitis' of animals. The bone appeared to be formed in the interstitial connective tissue of the lung, including the interalveolar septa. The sections of the autopsy showed more calcification than ossification."

Discussion

Pulmonary calcification and bone formation as a manifestation of lung disease has been discussed since the days of Virchow. He thought that the calcium deposits in the lungs and the stomach represented direct calcification of the tissues by lime salts of the blood which penetrated and filled the tissues. Wells stated that in this condition calcium salts are deposited throughout the body in apparently perfectly normal tissues, but especially in the lungs, kidneys and the gastric mucosa. These are sites where excretion of acids causes a more alkaline reaction in the subsurface tissues concerned and results in precipitation of calcium salts. These are less soluble because of the lowered concentration of hydrogen ions in the tissues. In other words, metastatic calcification, or calcinosis, is a condition in which calcium salts are deposited in tissues previously normal but where there is a tendency toward alkalinity, as in the lungs, kidneys and stomach.

Dystrophic calcification refers to a disturbance in which lime salts impregnate tissues, previously the seat of tuberculosis, histoplasmosis, suppuration, and other chronic diseases. A clear distinction between the two forms of calcification is not always possible since combinations have been found in some cases. Necrotic tissue is associated with increased alkalinity because of the lowered CO_2 tension, thus favoring precipitation of calcium phosphate. Bone disease, benign or malignant, has been known to have associated calcifications in the lungs with calcium deposits found in alveolar walls, veins, arteries, capillaries, bronchi and bronchioles. Chronic renal disease may be a cause of pulmonary calcification.

In these cases secondary hyperparathyroidism usually develops with enlargement of the parathyroid glands with diffuse hyperplasia of the chief cells. Frequently, the systemic arteries show calcification changes. Primary neoplasm of the parathyroid glands may produce, among other changes, calcification in the lungs. Sarcoidosis and hypervitaminosis D may be the cause of pulmonary calcinosis. Prolonged and excessive intake of absorbable alkali and milk may cause hypercalcemia and metastatic calcification without renal insufficiency (Burnett syndrome). A number of various conditions, such

as scleroderma, may have associated calcifications in soft tissues but not in the lungs.

MULLIGAN considered several factors involved in metastatic calcification.

In the calcification of the lungs, the calcium salts are precipitated in the tissues especially prone to be alkaline because of low carbon dioxide content, or conversely, because of high oxygen content of the blood bathing them, such as the capillaries of the alveoli, the venules and the veins of the lungs, the left chambers of the heart and systemic arterial tree.

In those organs in which acids are excreted, such as the lungs (CO_2), the gastric mucosa (HCl) and the kidneys (acid PO_4), the tissues are rendered alkaline and similar precipitation of calcium salts occurs.

Since serum is normally saturated with respect to $CaHPO_4$ and an alkaline Ph favors the holding of this compound in solution, $CaHPO_4$ is changed to $Ca_3(PO_4)_2$ and $CaCO_3$ for deposition in the soft tissues.

The diffuse form of pulmonary ossification occurs in two forms, *racemose* or branching and *nodular* or circumscribed. A third form, described by COHN, is not diffuse but localized and probably not related to other forms.

The *racemose* form is the commonest and consists of branching spicules of true bone running in the septa of the lungs, often continuous for some distance, but with isolated spicules. Usually the process is limited to certain areas and is not truly diffuse. About 35 cases of this type have been described, occurring almost exclusively in men of advanced years.

The best explanation of this form was advanced by DAUST. He stated that it appeared to be merely a metaplasia due to senile alterations in perivascular connective tissue. First, the vascular media degenerates, followed by marked perivascular connective tissue swelling and hyalinization. Thereafter, nuclei appear in the hyaline tissue. They are short and compressed, with dendritic processes, and apparently they form osteoid tissue which becomes calcified with formation of bone. He speaks of preliminary calcification leading to bone formation, but this metaplasia of calcification to bone is not adequately described or explained in any of the available publications. It is possible that a hyaline matrix of osteoid tissue is converted into true bone by the deposition of calcium. Marrow formation is occasionally observed in this new bone, but apparently it is much more rare and sparse than that commonly found in bone resulting from calcification of tuberculous scars, or in ossified bronchial cartilage. This form is not recognized roentgenologically.

The *nodular*, *circumscribed* or *tuberose* form of ossification is different both anatomically and in the class of patients involved, for it affects chiefly relatively young persons with mitral stenosis.

Since this condition is observed almost exclusively in association with mitral stenosis, one would expect it to be associated with calcium-iron incrustations,

but these do not seem to be a precursor of the ossification, except perhaps in a case reported by MUNK in which calcified elastic tissue elements heavily impregnated with iron as well as ossified plaques were found. This form should be recognized roentgenographically.

Nodular circumscribed ossification seems to be the result of connective tissue proliferation, both interstitially and within the alveoli. This would suggest interstitial pneumonia as the forerunner, were it not for the fact that in most of the cases it occurred in the lungs, the seat of chronic passive congestion from mitral stenosis. Histologically, the lungs show marked thickening of the alveolar walls, not only with connective and elastic tissue increase, but sometimes, conspicuously, with increase of nonstriated muscle fibres. There is also usually observed within the alveoli an exudate of homogeneous fibrinoid material in various stages of organization. The bone occurs as lamellae with thin small plaques, or as larger alveolar connective tissue. No calcification is observed to precede the ossification, but rather first osteoid tissue is formed in which calcium salts are deposited.

It should be noted that in metastatic calcification in the lungs, the calcium deposits do not undergo ossification. This is agreed by all workers on the subject.

A combination of chronic interstitial pneumonia with chronic pulmonary congestion might be instrumental in bringing about the tuberous type of ossification which is considered by TERPLAN to be the result of thrombosis in the septal capillaries. Bone spicules are not rare in the lungs of elderly persons with interstitial fibrosis of long duration. These spicules are present interstitially and are not the result of osseous metaplasia in bronchial cartilages. The early stage of the lesion has the appearance of osteoid tissue. Marrow can be formed in the fully developed bony masses. In the described cases of chronic interstitial pneumonitis and fibrosis with bone formation in elderly persons, one may reasonably assume that a high incidence of pulmonary congestion due to left heart failure, latent or clinical, usually occurs. Were it not that in nearly all the cases of ossification of this type there had been associated chronic cardiac decompensation, it would seem as if the decompensation had nothing to do with it. The possibility remains that the conditions favorable for ossification in chronic interstitial pneumonitis are present only when pulmonary congestion is added to the picture.

There is considerable evidence that venous stasis or general circulatory impairment favors bone formation provided that other conditions favorable to ossification are present. ENGELSTAD experimentally produced roentgen pneumonitis in rabbits and found pulmonary ossification similar to that observed with mitral stenosis. He stated that at least half of the animals examined two months or more after irradiation had more or less widespread ossification in the form of small disseminated particles of bone. His photomicrographs resemble human material in cases of ossification associated with mitral

stenosis. The susceptibility of the rabbit to calcification is well known and i explained by the high blood calcium which has been found to be from 12.4 t 18.4 mg per 100 ml.

No increased calcium is found as a constant occurrence in chronic passiv congestion of the lungs, but it might be that in occasional cases a rise in carbo dioxide is responsible for an increase in blood calcium. Ossifying pneumonit is common in the horse. Bone may be found interstitially in the lungs of oth animals. Calcification and osseous transformation of the cartilaginous rin of the trachea and bronchi is common in older persons (tracheopathia oste chondroplastica) and in chronic bronchitis at any age, whether or not associat with bronchiectasis. In some instances there may be a great hyperplasia of t cartilage and bone, and the lung may come to resemble the cancellous tiss of an epiphysis, grossly. The ossifying pneumonitis is distinctly different fro alveolar microlithiasis and alveolar proteinosis.

Our case presents several problems and questions, the answers to which a not easily understood. One question is whether the conditions of ossificati and calcification in the lungs are related. The extensive calcification in th arteries and the calcification of the gastric mucosa and kidneys with elevat serum calcium suggested a systemic condition as a cause. There was, howev no osteoporosis, and the parathyroids were not enlarged. Therefore, the possibility of hyperparathyroidism, primary or secondary, is considered unlikely. Burnett's syndrome cannot be exluded as an associated condition or predisposing factor.

The significance of the psittacosis is another question.

Psittacosis is an interstitial pneumonitis which may leave pulmonary fibrosis as a residual. It is reasonable to suggest in this case that it had produced a severe inflammation of the interstitial tissues of the lung which resulted in unusually marked interstitial fibrosis which became progressive. These changes impaired the already poor condition of the heart because of the arteriosclerosis of the coronary arteries and infarcts, resulting in chronic passive congestion. This further impaired the circulatory disturbance of the lungs and precipitated the massive calcium deposition and ossification. It is remarkable that the changes in the lungs appeared suddenly, within a brief period. The chest roentgenogram of an examination in May 1956 was reported negative, and about four weeks later the nodular lesions were recognized. Once the massive lesions were apparent, a very slight increase was observed until the death, as seen on reviewing the entire series of films.

The question whether the calcifications occurred first and some of them progressed into formation of bone cannot be answered, as discussed previously. However, this appears unlikely because the lung biopsy, performed several months before death, showed mostly bone formation in the interalveolar septa, and at the autopsy the calcifications were overwhelming. Therefore, we believe that the ossifying pneumonitis existed in the lungs even when the chest roent-

enograms were considered as essentially negative, since these fine bone spicules are not recognizable roentgenologically, and the chest lesions appeared suddenly when massive precipitation of calcium salts occurred.

It appears more likely that the two conditions may be independent, and in the case presented co-existed by chance, because predisposing factors for both conditions were present.

Acknowledgement

We are indebted to Doctor Averill Liebow for reviewing the pathology slides and for his kind suggestions, and to Doctor Lester S. King for the autopsy information. The case was referred by Doctor Oscar Comess.

SUMMARY

Pulmonary calcification and ossification is discussed on the basis of a report of a case of massive pulmonary calcification and bone formation.

ZUSAMMENFASSUNG

Pulmonelle Verkalkungen und Ossifikationen werden an Hand eines Falles von massiver Lungenverkalkung und Knochenbildung besprochen.

RÉSUMÉ

L'auteur étudie les calcifications et les ossifications pulmonaires en se basant sur un cas de calcification pulmonaire massive et de formation d'os.

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FROM THE CARDIOLOGIC LABORATORY (DIRECTOR: A. TYBJÆRG HANSEN) OF MEDICA
DEPARTMENT B (DIRECTOR: PROF. ERIK WARBURG), THE DEPARTMENT OF PAEDIA
RIC SURGERY (DIRECTOR: C. C. WINKEL SMITH) AND THE ROENTGEN DEPARTMEN
(DIRECTOR: PROF. GREGERS THOMSEN), RIGSHOSPITALET, COPENHAGEN, DENMAR

SUPRAPUBIC MICTURITION CYSTOGRAPHY WITH CONSTANT FILLING IN CHILDREN

by

J. BRYNDORF, E. ROSTGAARD CHRISTENSEN and E. SANDØE

Micturition cystography has until now suffered from the considerable drawback of being quite impracticable in infants and at the best a tedious affair. It is difficult to make the child micturate during the examination, and catheterization of the bladder during the postnatal period may be difficult or even impossible.

Owing to the fact that micturition cystograms are of special value in this age group for distinguishing between the different congenital urethral anomalies, we have elaborated a more timesaving and reliable method for cystometry in infancy and early childhood. The principle on which this new method is based is that the subject is made to micturate during the examination by continuous filling of the bladder with contrast medium through a catheter inserted into the bladder by the suprapubic route.

Bladder catheterization. The suprapubic catheterization, on which this method is based, was described in a former paper (SANDØE, BRYNDORF & GERTZ 1959). A cannula (ext. diameter 1.6 mm), a blunt piloting trocar (length 30 cm, diameter 0.8 mm) of nylon and a polythene catheter (length 20 cm, ex. diameter 1.6 mm, bore 1 mm) are used. The catheter is tapered at one en

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Fig. 1. Suprapubic region of a boy 6 years old, after puncture of the bladder, with the catheter in correct position.

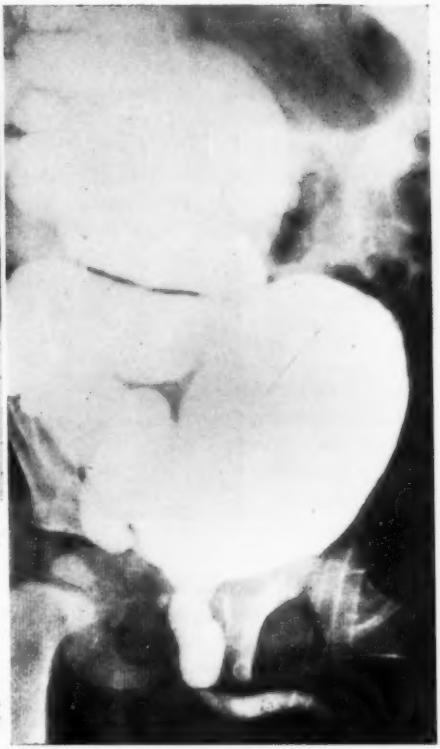

Fig. 2. Boy, aged 3 months, with chronical pyuria and urinary retention. Suprapubic cystometry revealed a valve in the posterior urethrae.

Fig. 2

so that it just slides over the nylon trocar and is furnished with a side hole 2 cm from the tip to ensure free passage of the contrast medium. A connector joins the other end of the catheter with a container holding contrast medium. Under local anaesthesia the bladder is punctured with the cannula 0.5 to 1 cm above the upper margin of the symphysis pubis in the midline. The nylon trocar is now inserted and the cannula removed and replaced by the catheter. The catheter and the trocar are together pushed into the bladder, after which the trocar is removed. The catheter is inserted 4 to 5 cm intravesically, if possible, and is then fastened to the skin and connected with the container (cf. Fig. 1). The procedure is a modified Seldinger technique and has been used by us for the catheterization of the peripheral arteries for the last five years (THOMSEN & TYBJÆRG HANSEN 1954).

Fig. 3. Boy, aged 18 months, with megacystis and megaureter caused by a urethral valve.

Radiologic technique. A detailed description of the radiologic technique, including the projections, contrast medium, and gonad doses was given in a previous paper on cystography with controlled filling pressure in children (ROSTGAARD CHRISTENSEN 1959).

Hypaque 45 % (sodium diatrizoate) in approximately a 12 % solution in sterile normal saline is used as contrast medium. The filling pressure is constant, the distance from the fluid level in the container to the symphysis pubis being 60 cm. The infusion of contrast medium (50 to 200 ml, according to the child's age) is started and is stopped just before micturition is expected and an a.p. film obtained. An interval of 30 minutes is allowed to elapse, if possible, before oblique views are taken, so that any delayed reflux may be demonstrated. The infusion is then resumed until the subject again voids, when as many micturition films as required, both obliques and true laterals, are exposed.

Material and Results. Twenty-six patients in all, 16 children and 10 adults, have been examined. The clinical diagnosis has always been recurrent pyuria or disturbance of micturition.

The new technique proved to be of great advantage in newborn babies and small infants compared with the methods used formerly, because all the

s bjects could be made to micturate during the investigation, and excellent r cturition films were obtained. Urethral valves were demonstrated in two o the children aged three and eighteen months (Figs 2 and 3). Good cysto- g ams were also obtained in the adults and older children; but in our opinion q ite as satisfactory results could have been obtained with the transurethral t hnique.

No complications in connection with the examination have been observed. T this may be added that about sixty percutaneous bladder catheterizations h ve been performed to date in the cardiologic laboratory for the purpose o micturition cystometry without any sequelae.

Conclusion

The advantages in the method described are greatest in the postnatal period and early infancy because the infants can be made to void as required and are usually more relaxed during the investigation. Furthermore the urethra is not touched, and spasm, or the destruction of possible valves, is avoided. The method may also be preferred in older children and adults, for instance in cases of incontinence and in those in which catheterization is impossible or difficult. Suprapubic catheterization also makes it possible to combine the roentgenologic examination with micturition cystometry (BRYNDORF & SANDØE 1960) and the functional importance of any anomalies revealed by the cystogram can be evaluated at the same time.

Suprapubic catheterization itself is both easy and timesaving and appears to involve little risk.

SUMMARY

A micturition cystographic technique, of particular value in the newborn and in early infancy, is described. The method is quick and reliable and has to date been employed in 26 cases without complications.

ZUSAMMENFASSUNG

Eine miktionszystographische Technik, von besonderem Wert für die Neugeborenen- und frühe Kindheitsperiode, wird beschrieben. Die Methode ist rasch und zuverlässig und war bisher an 26 Fällen ohne Komplikation ausprobiert worden.

RÉSUMÉ

Les auteurs décrivent une technique de cystographie mictionnelle particulièrement intéressante chez le nouveau-né et dans la première enfance. Cette méthode est rapide et fidèle, et a été utilisée à ce jour dans 26 cas sans complication.

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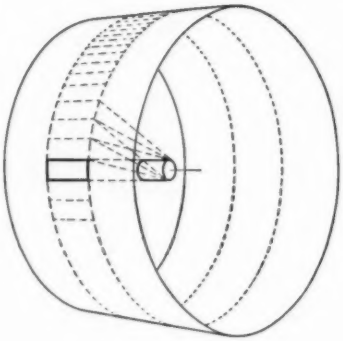

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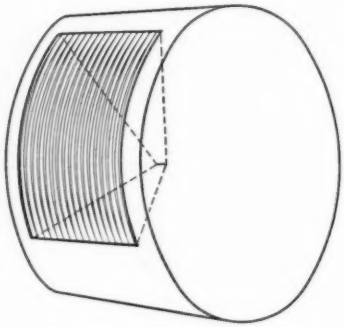

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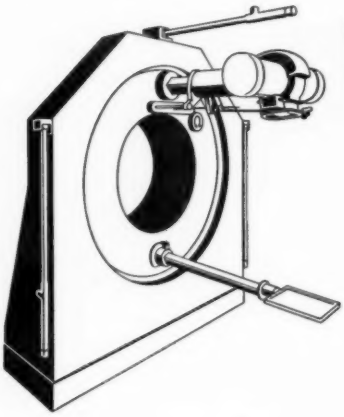

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METHOD FOR NON-DESTRUCTIVE DETERMINATION OF INORGANIC AND ORGANIC MATERIAL IN MINERALIZED TISSUES

by

K.-Å. OMNELL, B. LINDSTRÖM, F. C. HOH and E. HAMMARLUND-ESSLER

Microradiographic methods have been used for quantitative analyses on a cellular level of the amount of inorganic material in bone and teeth. The only hitherto available procedure for absolute determinations consists of the elementary analysis of calcium utilizing the difference in the mass absorption coefficient on either side of the *K* absorption edge of calcium (ENGSTRÖM 1946, LINDSTRÖM 1955, RÖCKERT 1958).

All other methods give the mineral content of a specimen expressed as the amount of a reference material of known roentgen absorption (AMPRINO and ENGSTRÖM 1952, OWEN 1956) where the amount of reference material may be transformed into an amount of hydroxyapatite (ROWLAND, JOWSEY and MARSHALL 1959), or as the linear absorption coefficient of the specimen (HOLMSTRAND 1957, WALLGREN 1957, NILSONNE 1959). Polychromatic roentgen radiation can be used for the former procedure, while the latter method requires relatively monochromatic radiation, the wavelength of which should be such that the absorption in the organic fraction of mineralized tissues can be neglected. The thickness of the specimens must also be determined, mainly by the microscopic measurement of the profiles of the cut and tilted specimens. The degree of

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mineralization is expressed as the amount of inorganic material per unit volume. These methods do not permit accurate determinations of the inorganic content of low-mineralized structures in which the absorption of organic material contributes considerably to the total absorption.

From a biologic point of view it is unsatisfactory to neglect the organic phase and express the degree of mineralization simply as the amount of bone salt per unit volume. Quantitative determination in situ of the organic content as well (without chemical separation of the two main components) in dehydrated mineralized tissue is therefore preferable.

The present study is concerned with a microradiographic procedure permitting a non-destructive quantitative analysis on a cellular level of both the organic and the inorganic components in mineralized structures.

Theory

Dehydrated mineralized tissue may be regarded as a mixture of hydroxyapatite and protein, mainly collagen. Two phases in a given specimen can be quantitatively determined by dichromatic roentgen absorption measurements, provided the ratio between the mass absorption coefficients of the two phases is not the same at the two wavelengths. The greater the difference between these ratios, the more sensitive is the method. The radiation must be chosen within an energy range where the absorption images of the specimens are suitable for photometric evaluation. Due consideration must also be paid to the specimen thickness obtainable with reasonable effort by conventional methods. For the analysis of mineralized specimens the wavelength range between 1 Å and 10 Å is suitable.

For one wavelength the ratio between the mass absorption coefficients of hydroxyapatite and collagen should be relatively high, and this wavelength must then be shorter than that corresponding to the K absorption edge of calcium ($\lambda_{K(Ca)} = 3.07$ Å). Within this wavelength range the high absorption of hydroxyapatite compared with that of collagen is due to the appreciable K absorption in calcium and also in phosphorus. Here, K radiation from elements with atomic number $Z > 20$ provides adequate monochromatic radiation. In this case vanadium ($Z = 23$) and chromium ($Z = 24$) are suitable anode materials. In the present study chromium $K\alpha_{1,2}$ radiation ($\lambda_1 = 2.29$ Å) was used.

For the other radiation the ratio between the mass absorption coefficients of hydroxyapatite and collagen should be relatively small, which occurs when neither calcium nor phosphorus has any photoelectric absorption in the L electron orbit, i. e. for radiation with wavelengths longer than the K absorption edge of phosphorus ($\lambda_{K(P)} = 5.79$ Å). In the present investigation zirconium $L\beta_1$ radiation ($\lambda_2 = 5.84$ Å) was used, there being no suitable K radiation within this wavelength range.

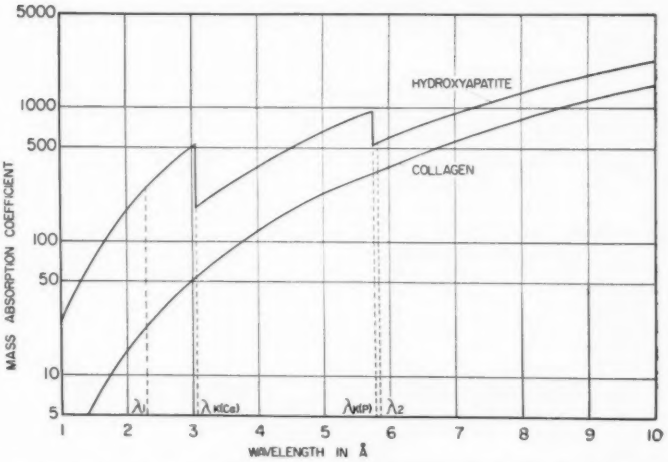

Fig. 1. The mass absorption coefficients of hydroxyapatite and collagen plotted against the wavelength of the roentgen radiation, showing the principle of the dichromatic microradiographic procedure.

The elementary compositions of hydroxyapatite, collagen, and methyl methacrylate are given in Table 1. In Fig. 1 the mass absorption coefficients of hydroxyapatite and collagen are plotted against the wavelength in the range 1 to 10 Å, the values being calculated according to HENKE, WHITE and LUNDBERG (1957). Since the values for methyl methacrylate practically coincide with those for collagen, no separate curve is drawn for the former.

Sections of mineralized tissues can seldom be prepared thinner than 10 to 15 μ, and therefore areas in the microradiograms corresponding to the direct incident radiation, and areas corresponding to absorption images of mineralized specimens, often differ considerably in density. For the best fine-grained photographic emulsions the density is proportional to the intensity of the incident roentgen radiation up to a value of about 0.5 (LINDSTRÖM 1955). The optical

Table 1

Elementary composition and density of hydroxyapatite, collagen, and methyl methacrylate

	% H	% C	% N	% O	% S	% P	% Ca	g/cm³	Reference
Hydroxyapatite	0.2	—	—	41.4	—	18.5	39.9	3.1	
Collagen	6.7	50.2	18.2	24.3	0.6	—	—	1.3	FLASCHENTRÄGER and LEHNARTZ (1951)
Methyl methacrylate	8.0	60.0	—	32.0	—	—	—	0.94	HODGMAN (1953)

transmission in the image of mineralized structures would therefore be too high to permit sufficient accuracy for photometry if only the straight portion of the density curve were utilized. With the use of a reference system, a step wedge of foils of known composition and known weight per unit area exposed together with the biologic object, the exponent in the general formula for roentgen absorption can be determined without measuring the photographic density. The photometer deflections for the image of the step wedge are then plotted against the number of steps. By means of this calibration curve the photometer deflection for the image of a given biologic structure is converted to a corresponding foil equivalent (see LINDSTRÖM 1955, Fig. 16). Since the photometer deflections corresponding to tissue structures are compared with the deflections for the different steps of the reference system, exposures exceeding those on the straight portion of the density curve may also be utilized.

Preliminary calculations showed that no available reference system with a limited number of steps could be used for both exposures. However, aluminium foils exposed to chromium $K\alpha_{1,2}$ radiation, and cellulose foils (elementary composition 9.8 % H, 64.5 % C, 10.3 % N, 15.4 % O) exposed to zirconium $L\beta_1$ radiation, could be used with advantage.

The experimental procedure may be expressed in the following way (OMNELL 1957)

$$(\mu/\varrho)_{\mathrm{Al}_1} f_{\mathrm{Al}} m_{\mathrm{Al}} = (\mu/\varrho)_{\mathrm{HA}_1} m_{\mathrm{HA}} + (\mu/\varrho)_{\mathrm{o}_1} m_{\mathrm{o}} \tag{1a}$$

$$(\mu/\varrho)_{\mathrm{c}_2} f_{\mathrm{c}} m_{\mathrm{c}} = (\mu/\varrho)_{\mathrm{HA}_2} m_{\mathrm{HA}} + (\mu/\varrho)_{\mathrm{o}_2} m_{\mathrm{o}} \tag{1b}$$

Here Al, c, HA and o indicate aluminium foils, cellulose foils, hydroxyapatite and collagen, respectively, and the indices 1 and 2 correspond to the wavelengths λ_1 and λ_2. Further, m_{Al} and m_{c} are the weights per unit area of one foil in the respective reference system, and m_{HA} and m_{o} are the weights per unit area of hydroxyapatite and collagen in the structure measured. The corresponding foil equivalents are denoted f_{Al} and f_{c}. From eqs (1a) and (1b) we obtain

$$m_{\mathrm{HA}} = \frac{f_{\mathrm{c}} m_{\mathrm{c}} (\mu/\varrho)_{\mathrm{c}_2} (\mu/\varrho)_{\mathrm{o}_1} - f_{\mathrm{Al}} m_{\mathrm{Al}} (\mu/\varrho)_{\mathrm{Al}_1} (\mu/\varrho)_{\mathrm{o}_2}}{(\mu/\varrho)_{\mathrm{HA}_2} (\mu/\varrho)_{\mathrm{o}_1} - (\mu/\varrho)_{\mathrm{HA}_1} (\mu/\varrho)_{\mathrm{o}_2}} \tag{2a}$$

$$m_{\mathrm{o}} = \frac{f_{\mathrm{c}} m_{\mathrm{c}} (\mu/\varrho)_{\mathrm{c}_2} (\mu/\varrho)_{\mathrm{HA}_1} - f_{\mathrm{Al}} m_{\mathrm{Al}} (\mu/\varrho)_{\mathrm{Al}_1} (\mu/\varrho)_{\mathrm{HA}_2}}{(\mu/\varrho)_{\mathrm{o}_2} (\mu/\varrho)_{\mathrm{HA}_1} - (\mu/\varrho)_{\mathrm{o}_1} (\mu/\varrho)_{\mathrm{HA}_2}} \tag{2b}$$

The values of the mass absorption coefficients in eqs (2a) and (2b) are given in Table 2.

The general absorption formula is valid only if the intensity of the re-radiation, associated with the absorption process, is extremely low, or if the main portion of this radiation is re-absorbed in the object. It has recently been shown that only the direct K fluorescence from elements with atomic numbers above 12 has any measurable influence on the microradiographic analyses of biologic

Table 2

Mass absorption coefficients of aluminium, cellulose, hydroxyapatite, and collagen at $\lambda_1 = 2.29$ Å and $\lambda_2 = 5.84$ Å

Substance	$(\mu/\rho)_1$	$(\mu/\rho)_2$
Aluminium	149	—
Cellulose	—	270
Hydroxyapatite	248	553
Collagen	23.9	322

specimens (HOH and LINDSTRÖM 1959). No appreciable direct K fluorescence is therefore emitted from a mineralized specimen and from cellulose foils on exposure to zirconium $L\beta_1$ radiation, and consequently eq. (1b) is valid without correction. In contrast, the re-radiation from a mineralized specimen and from aluminium foils on exposure to chromium $K\alpha_{1,2}$ radiation ought to be considered, and we actually obtain

$$I_{1(Al)} + \Delta I_{1(Al)} = I_o \cdot \exp\left[-(\mu/\varrho)_{Al_1} f_{Al} m_{Al}(1 + \Delta_{Al})\right] \tag{3a}$$

for the reference system, and

$$I_1 + \Delta I_1 = I_o \cdot \exp\left\{-\left[(\mu/\varrho)_{HA_1} m_{HA} + (\mu/\varrho)_{o_1} m_o\right](1+\Delta_{Ca})\right\} \tag{3b}$$

for the mineralized structure measured. Here, I_o is the intensity of the incident roentgen radiation, and $I_{1(Al)}$ and I_1 the intensity of the roentgen radiation transmitted through the step wedge of aluminium foils and through the specimen, respectively, when the re-radiation is neglected. Further, $\Delta I_{1(Al)}$ and ΔI_1 denote the intensity of the respective re-radiation, acting on the photographic emulsion, and Δ_{Al} and Δ_{Ca} the corresponding relative errors in the exponents. The experimental procedure implies that the left sides in eqs (3a) and (3b) are made equal photometrically, and consequently

$$(\mu/\varrho)_{Al_1} f_{Al} m_{Al}(1 + \Delta_{Al}) = \left[(\mu/\varrho)_{HA_1} m_{HA} + (\mu/\varrho)_{o_1} m_o\right](1 + \Delta_{Ca}) \tag{4}$$

To a very good approximation this expression can be transformed to

$$(\mu/\varrho)_{Al_1} m_{Al} f_{Al}(1 + \Delta_{Al} - \Delta_{Ca}) \approx (\mu/\varrho)_{HA_1} m_{HA} + (\mu/\varrho)_{o_1} m_o \tag{5}$$

The value of Δ_{Ca} has been calculated earlier for the wavelengths 1.54 Å and 2.50 Å (HOH and LINDSTRÖM 1959, Fig. 9), identifying Δ_{Ca} as $\Delta\mu/\mu$ in eq. (21) in that paper. In Fig. 2, $-\Delta_{Ca}$ is given as a function of the thickness of the mineralized specimen, exposed to chromium $K\alpha_{1,2}$ radiation, assuming the masses of inorganic and organic material to be roughly equal. The value of Δ_{Al} does not vary appreciably with variations in the composition of the specimen. On calculation of Δ_{Al} according to eqs (46) and (39) in the paper by HOH and LINDSTRÖM, the variation in the value of Δ_{Al} was found to be so small that the

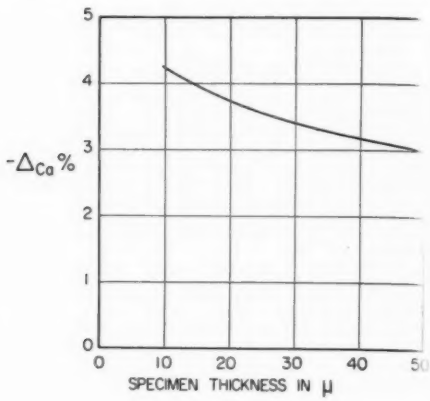

Fig. 2. The relative error introduced from the induced K fluorescence of calcium as a function of the thickness of the specimen (composition: protein ~ 45 % and hydroxyapatite ~ 35 % by weight).

relative error may be considered constant (— 0.7 %). Introducing the appropriate correction in eq. (1a) we substitute $f_{Al}\,(1 + \Delta_{Al} - \Delta_{Ca})$ for f_{Al}.

A detailed theoretical analysis of errors due to varying thickness and composition of the mineralized tissue will be given elsewhere.

The quantitative determination of mineralization

In principle the degree of mineralization of a tissue on a cellular level may be expressed in four ways, viz. amount of hydroxyapatite per unit of area, per unit of volume, per unit of total weight of fresh (not dehydrated) substance, and per unit of weight of dry substance. The organic content of the structure is not separately considered in the first, second or third procedure. The biologically important relation between the inorganic and organic components is expressed in the fourth procedure, which is advantageous in many cases. The first and second one permit the use of various preparatory methods and are therefore used most widely. The first but not the second requires sections of even thickness. However, the thickness of the specimen must be determined when applying the second procedure.

The third method is mainly of theoretical interest, it being extremely difficult to keep the water phase intact during the analytic procedure.

On application of the fourth method, the organic phase should preferably be kept unchanged. This can be secured by freeze-sectioning followed by freeze-drying. The use of this procedure might therefore be limited mainly to low-mineralized structures, but it does not require determination of the thickness of the specimen.

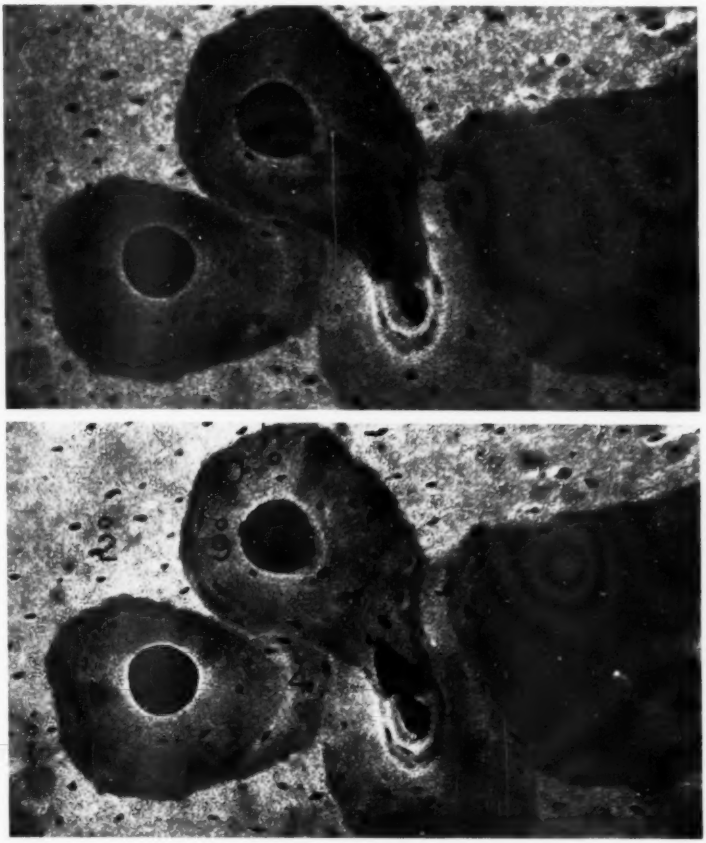

Fig. 3. Microradiograms of human adult compact bone, embedded in methyl methacrylate, upper view registered at $\lambda_1 = 2.29$ Å, and lower at $\lambda_2 = 5.84$ Å. Specimen thickness ~ 20 μ, secondary magnification 210×. The amounts of hydroxyapatite in mg·cm^{-2} in the measured areas (1) to (12) are: (1) 1.31, (2) 1.51, (3) 1.14, (4) 1.13, (5) 1.24, (6) 1.24, (7) 1.22, (8) 1.23, (9) 1.06, (10) 0.78,(11) 1.13, and (12) 0.93.

Experimental method. In the present methodologic study freeze-sectioning (20 to 40 μ) was performed according to ULLBERG (1954). Methyl methacrylate-embedded specimens were also studied. After dehydration in ethanol the specimens were embedded in vacuo. They were sawn into slabs which were ground plano-parallel with diamond powder to a final thickness of about 20 μ.

Fig. 4. Microradiogram of freeze-sectioned and freeze-dried primary bone from new-born dog registered at $\lambda_2 = 5.84$ Å. Specimen thickness ~ 30 μ, secondary magnification 195 ×. The ratios between amount of hydroxyapatite and total amount of dry substance in the measured areas are: (1) 0.47 and (2) 0.44.

The sections were exposed to monochromatic roentgen radiation in a high vacuum spectrophotometer with a cylindrically bent quartz crystal. The radius of curvature of the crystal was 200 mm, the spacing being 3.34 Å. Readers interested in a detailed description of the apparatus, are referred to LINDSTRÖM (1955). Utilizing chromium $K\alpha_{1,2}$ radiation a step wedge of aluminium foils was exposed together with the section, the weight per unit area increasing by 2.31 mg·cm^{-2} per step. On exposure to zirconium $L\beta_1$ radiation the reference system consisted of cellulose foils increasing by 2.50 mg·cm^{-2} per step. Kodak High Resolution Plates were used for the contact microradiographic procedure and developed in a conventional way.

Only relatively large homogeneous areas, of an order of 100 μ^2, were measured photometrically. It was therefore possible to use the photometer described by HOLMSTRAND (1957). However, a detailed photometric analysis of smaller structures is in progress. The photometric data were evaluated according to eqs (2a) and (2b) with f_{Al} replaced by $f_{Al}\ (1 + \Delta_{Al} - \Delta_{Ca})$.

The *application of the method* is illustrated by some microradiograms representing bone specimens prepared according to the two main preparatory methods available. In Fig. 3 some Haversian systems are shown from cross sectioned compact human adult bone embedded in methyl methacrylate, the upper microradiogram taken with chromium $K\alpha_{1,2}$ radiation, and the lower with zirconium $L\beta_1$ radiation. There is a conspicuous difference in absorption

etween the Haversian systems and the surrounding lamellae. However, ere are also considerable differences in absorption within the osteons. n the lower microradiogram some measured points are plotted, and orresponding values of the amount of hydroxyapatite in $mg \cdot cm^{-2}$ are ven.

Part of a freeze-sectioned and freeze-dried transverse section of the femoral aphysis of a new-born dog is shown in Fig. 4. The appearance is typical of imary bone. Two of the measured points are plotted, and the values given the legend represent the ratio between the inorganic component and the tal amount of dry substance.

Discussion

Owing to the difficulty in obtaining sufficient intensities, monochromatic roentgen radiation has rarely been utilized in microradiographic investigations of bone. However, monochromatization has several advantages in quantitative microradiographic research. Filtration of polychromatic radiation in the object may introduce serious errors in quantitative analyses, partly because of the varying response of the photographic emulsion to different quantum energies. Monochromatic radiation excludes this error. If a reference system is used, the ratio between the mass absorption coefficients of the object and the reference system may vary with the wavelength of the radiation without introducing any source of error, which considerably simplifies the choice of reference material.

According to the dichromatic procedure in the present study it is possible to make accurate quantitative determinations of the inorganic fraction of mineralized tissues, the contribution of the organic material to the absorption being determined either separately in the study of freeze-sectioned and freeze-dried material, or in combination with the embedding medium in the investigation of methyl methacrylate-embedded specimens. The inorganic fraction can therefore be related to the total dry weight in freeze-sectioned specimens, but in embedded specimens the mineralization must be expressed per unit of area or per unit of volume. The latter procedure requires determination of the thickness of the specimens. The analytic procedure is however essentially non-destructive, so that the influence of decalcifying methods on the organic phase may be studied in freeze-sectioned specimens. Furthermore, analysis of the phosphorus may be performed if the section is also exposed to monochromatic radiation with a wavelength lying on the short wavelength side of the K absorption edge of phosphorus.

Previous microradiographic investigations of bone and teeth have mainly determined the distribution of the mineral but the present method permits a non-destructive determination of the distribution of the organic material as well.

Acknowledgement

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SUMMARY

The theoretical background for quantitative analyses of organic and inorganic components in sections of mineralized tissues employing dichromatic microradiography is given. The technical procedure is briefly described and some examples are given of the application of the method to analyses of freeze-sectioned and freeze-dried bone and of plastic-embedded ground-sectioned bone.

ZUSAMMENFASSUNG

Die theoretische Grundlage der quantitativen Analyse von organischen und anorganischen Komponenten in Schnitten mineralisierter Gewebes bei Anwendung dichromatischer Röntgenmikrographie wird besprochen. Es wird die technische Ausführung in groben Zügen beschrieben und einige Beispiele über die Anwendung der Methode für Analysen von Schnitten gefrorenen, getrockneten und in Plastmasse eingebetteten Knochens gegeben.

RÉSUMÉ

Les auteurs exposent les bases théoriques de l'analyse quantitative des composants organiques et inorganiques dans les coupes de tissus minéralisés au moyen de la microradiographie dichromatique. Ils décrivent brièvement la technique et donnent des exemples de l'application de cette méthode à l'analyse d'os coupé en congélation et desséché en congélation et d'os inclus dans un plastique et coupé par abrasion.

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FROM THE DEPARTMENT OF ANATOMY OF THE VETERINARY COLLEGE, AND THE RADIOTHERAPY CLINIC OF THE HELSINKI UNIVERSITY, FINLAND

EFFECTS OF WHOLE-BODY ROENTGEN IRRADIATION ON THE NEUROSECRETORY MATERIAL OF THE RAT NEUROHYPOPHYSIS

by

V. K. Hopsu, S. Talanti and A. Voutilainen

As first suggested by Scharrer (1928), it is now generally held that the nucleus supraopticus and nucleus paraventricularis of the hypothalamus possess secretory activity. The secretion from the secretory neurones migrates along the neural tracts into the neurohypophysis; it tends to gather around the capillaries and may possibly be released into the circulation.

The neurosecretory phenomena are mainly revealed by morphologic examination of the hypothalamo-hypophyseal system. Bargmann (1949) was the first to show that the 'secretion' could be stained selectively by the Gomori (1941) chrome-haematoxylin method, and that it appeared as a granular material. Certain other staining techniques, e.g. with aldehyde-fuchsin (2) and Alcian-blue (14) have proved more recently also to be selective.

The physiologic significance of neurosecretion in vertebrates is less well understood. With some experimental procedures changes in the amount of secretory material have, however, been produced and the concept of the function of the secretion is based on these findings. Under conditions of chronic water deprivation, loss of the neurosecretory material from the hypophysis is produced (9) and the material returns when the animals are again given water (13). The substance is also quantitatively decreased in rats with alloxan diabetes (7). Rothballer (1953) demonstrated that a painful stimulus caused loss of neurosecretory material in the hypophysis in the rat.

Experimental investigations suggest that the neurosecretory material contains an antidiuretic agent or its 'carrier' substance. Wherever the material

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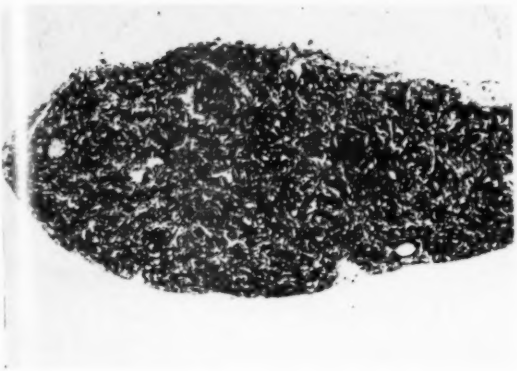

Fig. 1. Sagittal section of the neurohypophysis of a control rat. Neurosecretory material homogeneously distributed. Aldehyde-fuchsin. × 100.

is found, proportional amounts of neurohypophysis hormones can be detected (6). It has been observed that the material is absent in human diabetes insipidus (3). It is also diminished in pyometra in the dog, in which marked polydypsia and polyuria occur (15).

The purpose of this investigation was to determine whether changes in the amounts of neurosecretory material occurred in test animals exposed to whole-body roentgen irradiation. In previously performed investigations (10) definite polyuria could be established after whole-body irradiation. It was most marked 5 and 6 days following irradiation. If the neurosecretory material contained an antidiuretic agent, changes could be assumed in the amount of material at this time.

Material and Methods. Twenty-two rats in all were employed, 13 belonging to the test group and 9 rats serving as controls.

The group of test animals was exposed to whole-body roentgen irradiation in a dose of 500 r, the factors being 180 kV, 15 mA, filtration 0.5 Cu, FSD 60 cm, and HVL 1.05 Cu. The animals were killed after 6 days by decapitation without anesthesia. The control group was kept under similar conditions, and in the same room at a temperature of 18° C, and given the same food. They were killed in similar fashion and at the same time as those of the test group.

After decapitation the hypophyses were removed, fixed in 10 % formalin for 72 hours, and embedded in paraffin. All sections were cut at 5 μ in the sagittal plane and stained by the GOMORI (1941) aldehyde-fuchsin method as modified by LANDING et coll. (1956). The sections to be compared were always treated with the same stain under the same conditions.

The Fisher exact probability test was used for the statistical treatment of the results.

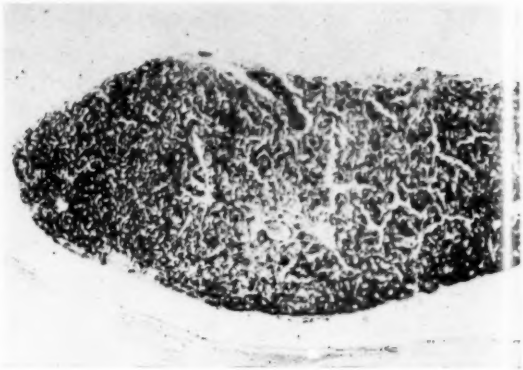

Fig. 2. Sagittal section of the neurohypophysis of an irradiated rat. Neurosecretory material decreased and more heterogeneously distributed. Aldehyde-fuchsin. × 100.

Results

The dark staining obtained of the sections of the control group made it easy to distinguish them. Neurosecretory material was abundant and was distributed evenly throughout the hypophysis (Fig. 1). The sections of the irradiated rats were considerably different from one another. The amount of stainable material seemed to vary from normal to sparse; in addition, in some sections the distribution of the material was heterogeneous (Fig. 2).

Since no histoquantitative methods are available by which the amount of stainable neurosecretory material could be determined objectively, it had necessarily to be estimated subjectively. The investigator compared sections through the hypophysis of the irradiated animals with corresponding sections of the control group without knowing to which group the section belonged. The sections were divided into two types: one with 'normal' dark staining and rich in stainable material, the other with lighter staining and scanty material.

The results obtained were as follows, the figures indicating the number of rats:

Neurosecretory material	Decreased	Normal	Total
Irradiated rats	8	5	13
Control rats	0	9	9

In this case the change is significant at the level $P < 0.05$.

Discussion

Whole-body roentgen irradiation produced an apparent decrease of neurosecretory material in the neurohypophysis. Under similar experimental conditions in rats it has previously been shown that diuresis increased (10). This

is confirmed by the present results and favours the view that neurosecretion plays a role in the regulation of water metabolism. The increase of diuresis and the decrease of neurosecretory material are apparently two parallel phenomena. Our results add further support to the concept that the neurosecretory material is the morphologic equivalent of the posterior lobe hormones.

It is not possible to determine from the results the reason why the neurosecretory material decreases in amount. Since the neurohypophysis acts as a reservoir of material, the decrease of the latter is probably due to the rapid release of the supply into the circulation, or to the fact that the synthesis of material has lost its intensity in the hypothalamus. The latter alternative seems to be more likely. The decrease of material could be interpreted as resulting from the decrease in the activity of neurosecretory neurones induced by irradiation.

SUMMARY

Investigations showed that whole-body roentgen irradiation of 13 rats produced a decrease in the amount of neurosecretory material in 8 of the animals. No corresponding changes were detected in the control group. The relation between this observation and the polyuria previously reported under similar experimental circumstances is discussed.

ZUSAMMENFASSUNG

Untersuchungen zeigten, dass die Ganz-Körperbestrahlung von 13 Ratten bei 8 der Tiere eine Verminderung von neurosekretorischem Material zur Folge hatte. Bei der Kontrollgruppe waren solche Veränderungen nicht vorhanden. Die Relation zwischen diesen Befunden und Polyurie, über die schon früher unter ähnlichen Versuchsbedingungen berichtet worden war, wird diskutiert.

RÉSUMÉ

L'expérimentation a montré que l'irradiation corporelle totale de 13 rats par les rayons de roentgen a produit une diminution de la neurosécrétion chez 8 de ces animaux. On n'a pas observé de modifications semblables dans le groupe témoin. Les auteurs examinent la relation entre cette constatation et la polyurie qu'ils ont décrite précédemment dans des conditions expérimentales similaires.

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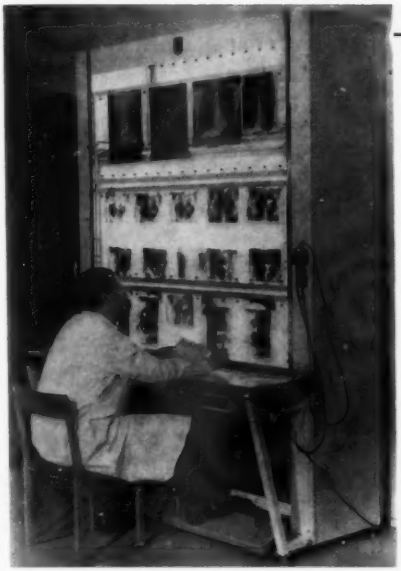

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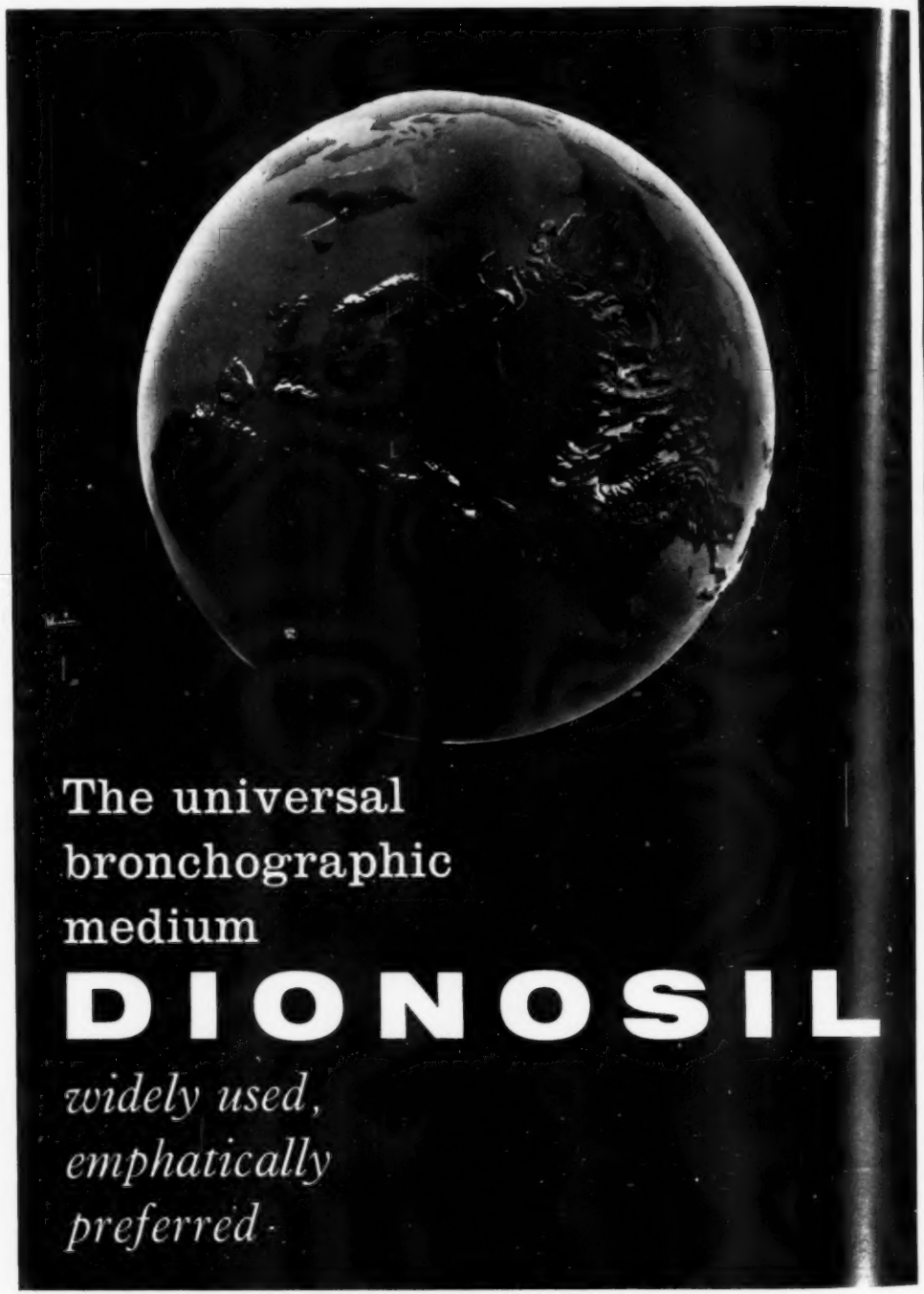

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IRRADIATION OF LIPOSARCOMA

by

MILTON FRIEDMAN and JOHN W. EGAN

The occasional report of favorable shrinkage following irradiation of an inoperable or recurrent liposarcoma prompted this analysis of twelve cases in order to define more accurately the role of irradiation in the management of this tumor.

Most series of cases had been reported by surgeons and pathologists who rarely included all the irradiation data needed for estimating the tumor dose in any given case. Some liposarcomas were said to be radiosensitive and irradiation was of value in their management. The efficacy of irradiation as an adjunct to surgery in the treatment of liposarcoma was stressed by PACK and PIERSON, who stated that among twelve patients treated with irradiation alone, two tumors were sterilized and six tumors shrank more than 50 % in size. Of the cases treated with pre-operative irradiation, 60 % regressed partially and 15 % apparently shrank completely. However, residual tumor cells were found in most of the resected specimens. PACK reported a 5 year survival rate for lesions treated by excision and postoperative irradiation of 87.5 %, whereas with local excision it was 50 %. No mention was made in this report of the histologic types, their respective radiosensitivity or the irradiation dosage employed.

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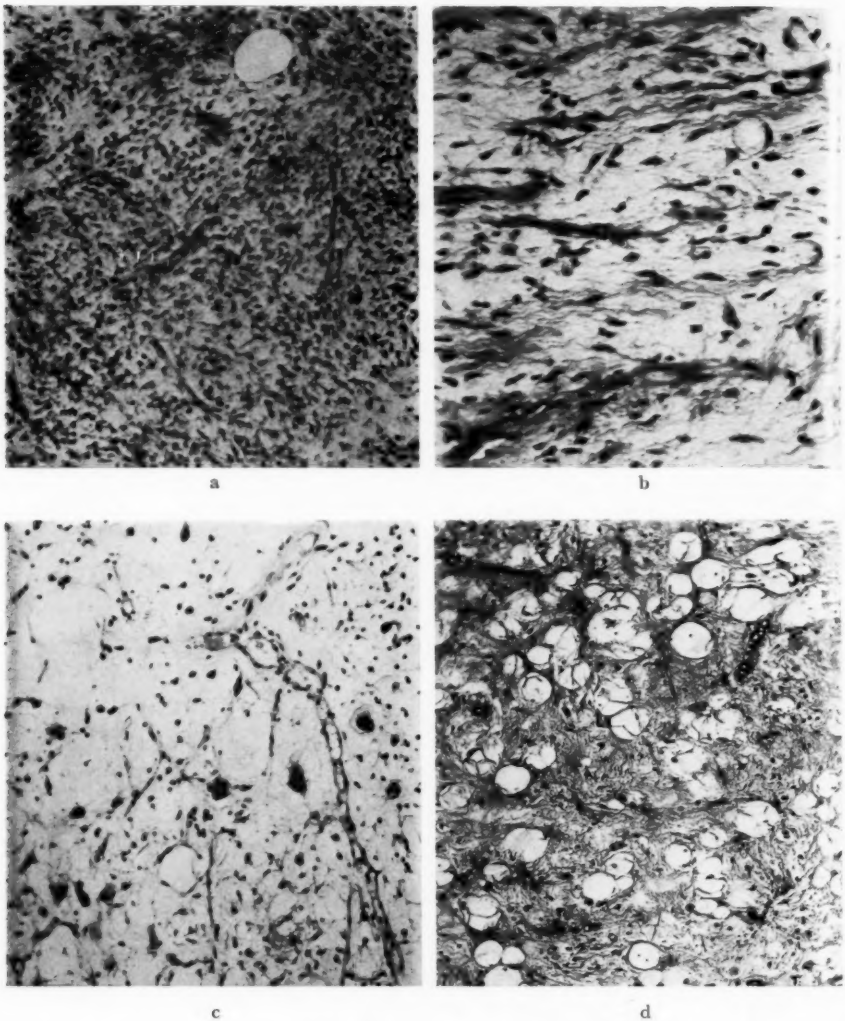

Fig. 1. Liposarcoma, type I. Well differentiated myxoid type, moderately radiosensitive.

a) Case 8, × 125. Spindle-shaped cells with fat droplets, resembling myxosarcoma. Characteristic rich network of large and small capillaries.

b) Case 8, × 225, high power view of same tumor.

c) Case 2, × 125, moderately differentiated myxoid type with pleomorphic cells. All the typical features: adult fat cells, stellate and spindle-shaped lipoblasts, and myxoid connective tissue with capillaries. Resembles embryonal fat.

d) Case 12, × 125, retroperitoneal liposarcoma of clinically short duration, but hyalinized stroma suggests chronic course. Nevertheless moderately radiosensitive.

Of the four irradiated tumors reported by MORELAND, there was no response in three, and in one patient irradiated prophylactically after excision, there was no recurrence 4 years and 9 months later.

In the eight irradiated cases reported by STOUT (1944), there seemed to be some interdependence between histologic type and radiosensitivity. Three lesions were undifferentiated myxoid liposarcoma (type II); in one there was complete regression of a recurrent lesion for seven and one-half years; in the second there was partial regression; the third patient, irradiated prophylactically after operation, had a very short follow-up period. Two other lesions were round cell liposarcoma (type III) and two of a mixed round cell and undifferentiated cell type. In none of these was there any significant response to irradiation. Unfortunately it was difficult to estimate the tumor doses from the data presented.

We therefore undertook to study further the relation between histology and response to irradiation, and to estimate the tumor dosage required to achieve partial arrest and total destruction of the tumor.

Pathology

Twelve cases of liposarcoma were reviewed and an attempt made to fit them into the classification of STOUT (1944), as indicated in the following.

Type I: well differentiated myxoid (Fig. 1). This type resembles myxosarcoma. It consists of adult fat cells and regularly formed stellate or spindle-shaped lipoblasts containing lipoid droplets in a myxoid connective tissue stroma, usually with a rich capillary network and occasionally varied by the presence of well developed collagen and reticulin fibers. Mitoses are rare, the malignancy is very low grade, and it rarely metastasizes.

Type II: poorly differentiated myxoid (Figs 2 and 5a). This type which may resemble type I but has bizarre lipoblasts with hyperchromatic or pyknotic nuclei and a less prominent vascular network. Adult fat cells are rarer and areas resembling fibrosarcoma may be present.

Type III: undifferentiated round cell (Figs 3, 4 and 5b). This type has centrally placed nuclei and foamy or granular cytoplasm filled with lipoid. The cells may reach an enormous size. The delicate fibrous stroma is scant and the vascular pattern is not conspicuous. The stroma is no longer myxoid and the cells are usually in fairly close juxtaposition.

Type IV: mixed (Fig. 5). This type is composed equally of two or more elements of the above groups. A high percentage of liposarcomas are of the mixed type.

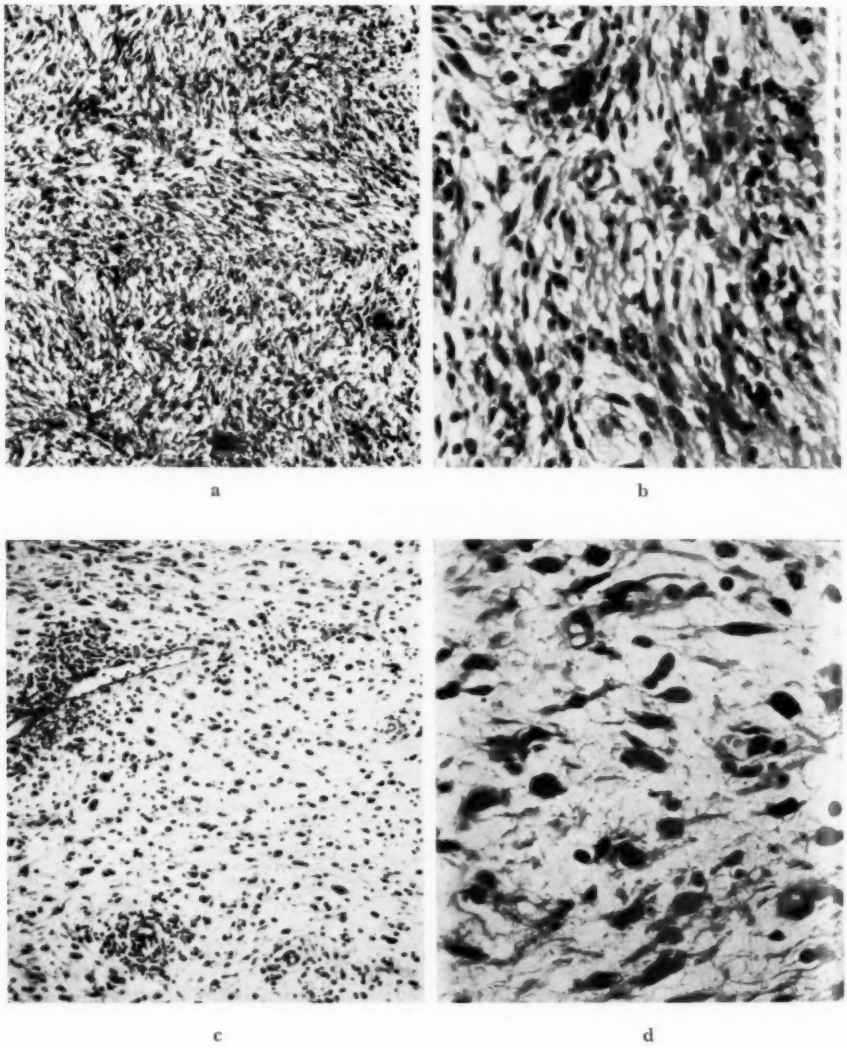

Fig. 2. Liposarcoma, type II. Poorly differentiated myxoid type, moderately radioresistant. All photomicrographs taken from the same patient (Case 1).

a) and b) Low power (× 125), and high power (× 225), photomicrographs before irradiation. The tumor resembles fibrosarcoma, but the cells contain fat. Giant hyperchromatic bizarre lipoblasts are common. c) and d) Low power (× 125) and high power (× 225) photomicrographs of the same tumor, removed by amputation 3 days after a tumor dose of 2 300 rads in 11 days. There were slight radiation changes in the cells with no destruction of any cells.

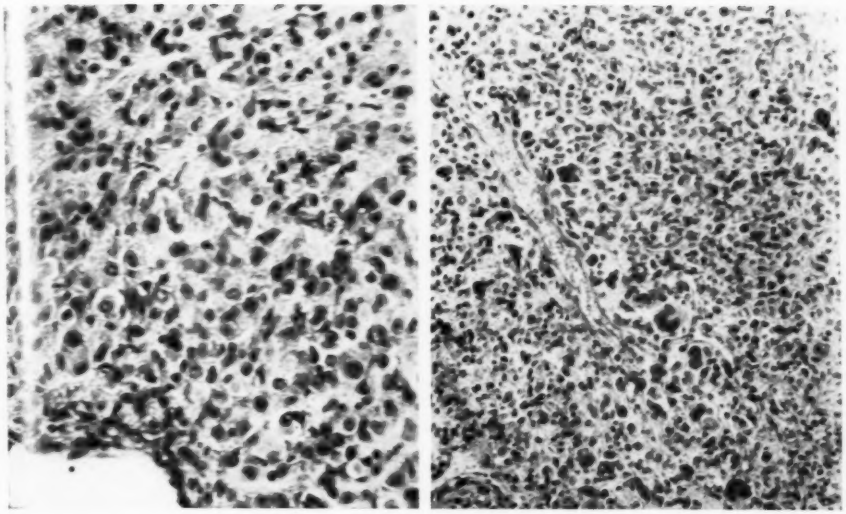

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Fig. 3. Liposarcoma, type III. Round cell or adenoid type of liposarcoma. This is highly malignant and radioresistant.

a) Case 10, × 225, rapidly growing tumor whose entire course from onset to death was 7 months. Marked cellularity, granular cytoplasm, central position of the nuclei and scant cytoplasm.

b) Case 7, × 125, slowly growing tumor of seven years duration and two operations prior to roentgen therapy. Tumor resembles that in fig. 3a but has in addition bizarre lipoblasts.

According to STOUT, type I may recur locally after excision but probably does not metastasize while in this form. Types II and III, besides being difficult to eradicate locally, may metastasize.

We attempted to fit our cases into these categories but two difficulties were encountered. The first was the differential diagnosis. Originally seventeen cases of liposarcoma were collected and reviewed with Dr. STOUT who questioned the diagnosis in five instances. The remaining twelve fell into the consistent pattern previously described. His diagnoses in the five eliminated cases were mesenchyma in two cases, rhabdomyosarcoma, myxosarcoma, and infiltrating reticulum cell sarcoma. The mesenchymomas contained various connective tissue elements, including liposarcoma and rhabdomyosarcoma. In rhabdomyosarcoma fat stains often showed abundant lipoid material (on which the original diagnosis of liposarcoma had been based). From the standpoint of cellularity the most commonly misinterpreted lesion, closely resembling liposarcoma, was rhabdomyosarcoma. Rhabdomyosarcoma has the additional

feature of being moderately radiosensitive, even more so than liposarcoma.

The second difficulty was that many liposarcomas contained varying mixtures of the three cell types. They were therefore classified according to the predominating cell type. Four cases were predominantly type I (well differentiated, myxoid); three cases were type II (poorly differentiated myxoid); four cases were type II (undifferentiated round cell); one case, finally, was in the 'mixed' group. The tendency is for the mixture to contain two adjacent types, i. e. I and II, or II and III. Seldom do types I and III appear in the same tumor; this occurred in one case (No. 3) in our series.

Irradiation

All lesions were irradiated with supervoltage (2 MV) roentgen rays, occasionally with the rotation technique.

In order to evaluate the accomplishments of irradiation, our data has been assembled in the Table on page 231. In the first group of three lesions wherein we aimed for cure, the doses of irradiation were very large, i. e. more than 9 000 rads. As a matter of fact, two patients sustained irradiation injury from these doses (Figs. 9 and 10), although both are alive four and five years, respectively, without evidence of tumor. These massive doses wiped out the chance of observing any difference in radiosensitivity due to histologic type in this group of cases.

The second group of two patients received smaller doses. One patient (Case 12 — Fig. 1d) with a massive retroperitoneal liposarcoma in the upper abdomen, type I, is alive six months after a moderate tumor dose of 6 770 rads in 79 days. The tumor has shrunk more than 75 % but the patient is weakened by irradiation gastritis. The other patient (Case 3) had a 6 cm metastatic mass on the chest wall, histologic type II. It was destroyed with a dose of 4 030 rads in 20 days, and did not recur during the remaining year of patient's life. These cases are examples of the effect of non-necrotizing doses in palliating liposarcoma. It is of interest that in the first two groups, where irradiation has been effective, the majority of lesions were of the lower grades of malignancy.

Liposarcoma is another one of the many exceptions to the law of BERGONIE-TRIBONDEAU (see FRIEDMAN 1957), in that the slowly growing, low grade of malignancy, the well differentiated type I is more radiosensitive than the cellular, highly malignant, undifferentiated type III.

In the third group of cases, two features are outstanding. Significant palliation of signs or symptoms have been achieved with tumor doses ranging from 3 000 to 4 000 rads; and four of the six lesions which showed good palliative response were in the moderately differentiated group (type II). Four other lesions which failed to respond to still smaller doses of irradiation, are not included in the table.

Table

Results produced by irradiation of liposarcoma patients

ase No.	Location	Predominant histologic type	Tumor dose (rads/days)	Duration of effect (years)
		Destruction of tumor		
3	Buttock	mixed	9000/31	4½
7	Thigh	3	9200/39	5
8	Thigh	1	9360/49	4
		Arrest for approximately one year		
12	Retroperitoneal..	1	6770/79	½
3	Chest wall	2	4030/20	1
		Partial regression or retardation		
11	Thigh	3	6720/24	70 % shrinkage for 1 month, amputation
6	Buttock	2	6000/22	Complete disappearance, recurrence in 1 year
6	Lung	2	4200/17	50 % shrinkage transient
4	Lung, right.....	2	3000/22	75 % shrinkage transient
4	Lung, left	2	3000/39	30 % shrinkage transient
3	Lung	3	3000/30	90 % shrinkage transient

The 'time-dose' points for fifteen lesions have been plotted in a scatter diagram (Fig. 6) which includes doses from the table and the four doses which were not effective against any tumor. The latter doses ranged from 1 400 rads in seven days to 3 840 rads in 25 days. Three of the four ineffective doses were delivered to type III undifferentiated, round cell liposarcoma, which paradoxically are the most highly malignant but the least radiosensitive.

Four additional sites in the twelve patients were irradiated prophylactically immediately following operation. They are not included in the present analysis because of the inability to observe the response of a demonstrable tumor to irradiation.

Case 3 yielded a great deal of information concerning radiosensitivity. The primary tumor in the buttock (Fig. 8) was the mixed type, being composed of all elements, but with predominant type II (Cf. fig. 5a). It was arrested with 9 000 rads in 31 days for four and one-half years until the patient died. The entire neoplastic process was rather highly malignant in behaviour and the duration prior to first treatment was only nine months. Ordinarily we would not expect the differentiated myxoid tumor to metastasize. In this case one of the metastases was a chest wall nodule, and a biopsy specimen was diagnosed: differentiated myxoid type I liposarcoma. A tumor dose of 4 030 rads in 20 days caused complete disappearance of that nodule. Another metastatic nodule

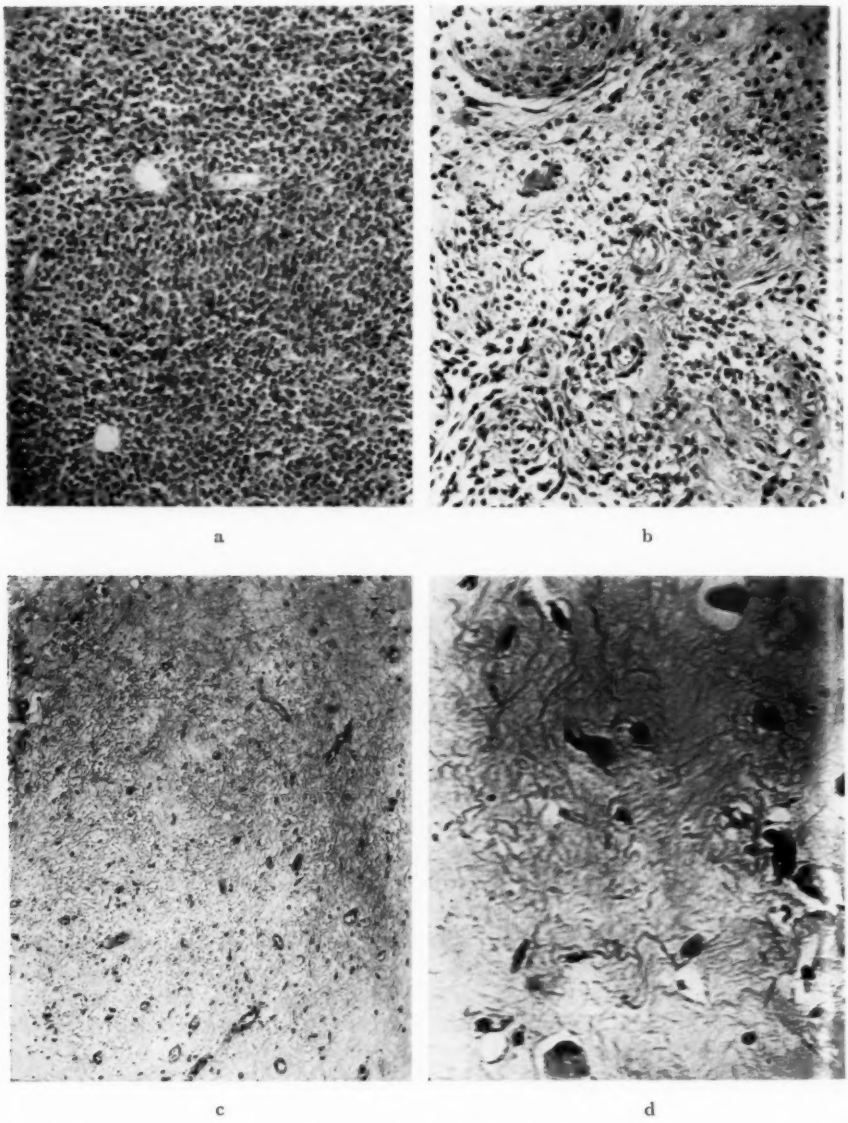
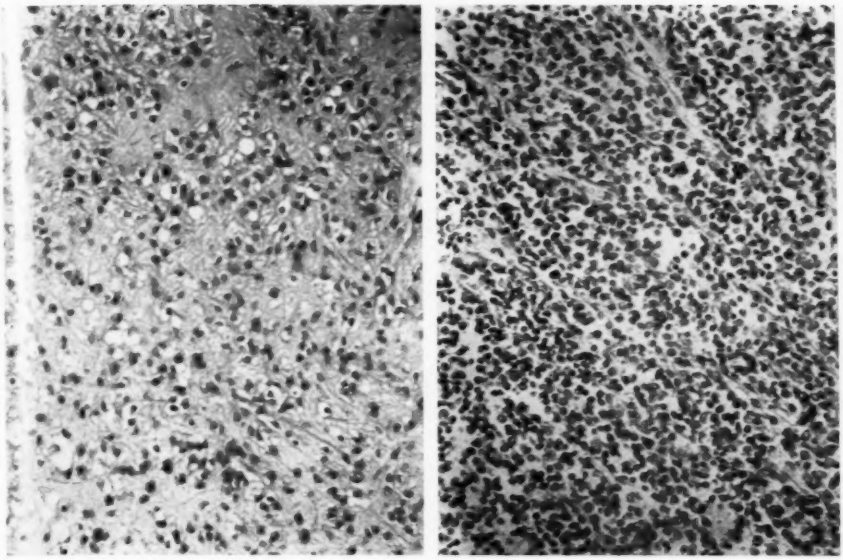


Fig. 4. Liposarcoma, type III. Another example of undifferentiated round cell liposarcoma (Case 11), before (a) and four weeks after 6 720 rads in 24 days (b—d).

b) × 125, liposarcoma cells mostly destroyed leaving behind adult connective tissue stroma and a few myxoid areas.
c) × 75, tumor destroyed leaving behind myxomatoid stroma and capillaries.
d) × 225, a few remaining lipoblasts in advanced stage of degeneration.



a b

Fig. 5. Mixed type (Case 3). a) Primary tumor in buttock, type II, poorly differentiated myxoid. This lesion did not recur during the 4 years following 9 000 rads in 31 days. b) Metastasis in lung, type III, undifferentiated round cell liposarcoma arrested transiently for only 6 months with 3 000 rads in 30 days.

in the lung was given 3 000 rads in 30 days and apparently disappeared, only to recur in four months. Subsequently the disease became very radioresistant especially terminally. Examination of the lung nodule at post-mortem showed an undifferentiated round cell type of liposarcoma which is the radioresistant variety (Fig. 5b).

In radiologic lore, it has been assumed that an occasional liposarcoma is radiosensitive and possibly radiocurable. However in the previously published cases, it is difficult to find a 5 year arrest of a tumor with irradiation only. STOUT (1944) reported a seven year arrest of a recurrent small lump in the leg with a dose of 6 000 r in 40 days. It is not certain whether this is tumor dose or air dose, probably the latter. STOUT (1953) also has stated that only small superficial tumors, 4 cm or less in diameter, have proved curable by irradiation. It is our experience that liposarcoma can be destroyed with irradiation, but in most instances with massive doses in the range of 7 000 to 9 000 rads.

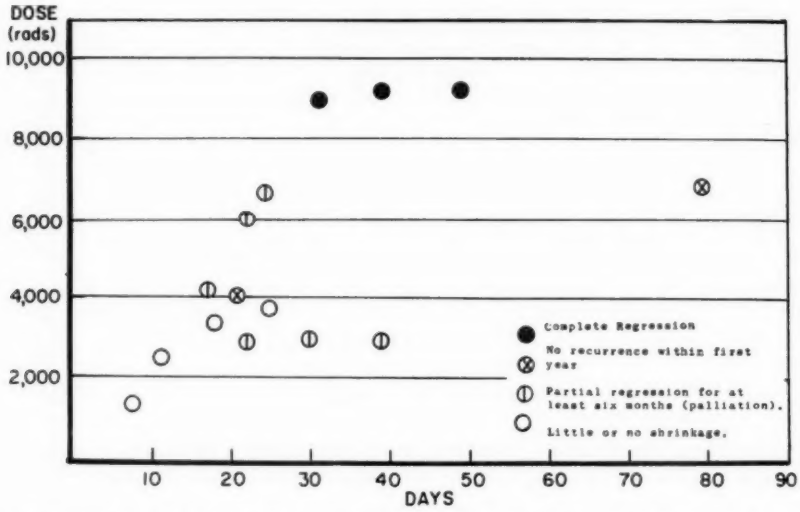


Fig. 6. Scatter diagram of doses administered to fifteen observable or demonstrable tumors in twelve patients. Four lesions, which were given postoperative prophylactic irradiation, are not included as there was no visible tumor for evaluation of response.

The opportunity to study histologic effects of irradiation on liposarcoma was afforded in two cases. In Case 1, a poorly differentiated myxoid type II lesion showed very slight radiation changes following a tumor dose of 2 300 rads in 11 days (See fig. 2).

On the other hand, Case 11, an undifferentiated round cell type III liposarcoma of the thigh, was given a tumor dose of 6 720 rads in 24 days. Although it was a radioresistant type, nevertheless one month later the tumor shrank 70 % in volume and a disarticulation was done. In the microscopic specimen (fig. 4) there was marked destruction of tumor cells and replacement fibrosis, but there were some residual islands of tumor cells resembling fibrosarcoma and also islands of myxoid tissue. It was expected that the fibrosarcoma-like areas would be radioresistant, but it was rather surprising to see the myxoid areas persist. On careful inspection of these myxoid areas one could assume that only the stromal architecture persisted. In many areas the myxoid cells were in advanced stages of disintegration.

Our general experience in irradiating many types of sarcoma of the soft somatic tissues has led to the opinion that among the more radiosensitive types, moderate doses (4 000 to 6 000 rads) may destroy most of the tumor but there always are a few mature parent cells which are radioresistant and from

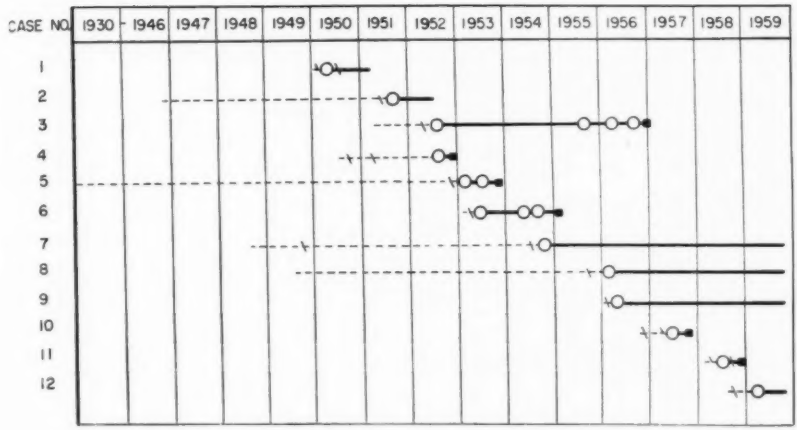


Fig. 7. Life history chart of 12 cases of liposarcoma. Cases No. 1 and 2 could not be traced after one year. Four patients were free of disease in November 1959. Cases No. 2, 8, 9 and 12 are histologic type I; No. 1, 4 and 6 type II; No. 5, 7, 10 and 11 type III; No. 3 is 'mixed'. The *dotted line* represents pre-treatment duration; *small slant line* — biopsy; *large slant line* — total or subtotal surgical extirpation; *circle* — supervoltage irradiation; *black square* — death; *solid horizontal line* — post treatment survival.

which a recurrence will grow. This may explain the wide disparity between the palliative dose of 3 000 to 4 000 rads and the curative dose of 8 000 to 9 000 rads (Fig. 6).

Longevity in patients with liposarcoma is generally related to histologic type. The life histories of the twelve cases are illustrated in Fig. 7. There are two classes, long-lived patients with tumors of low grade malignancy and short-lived patients with tumors of high grade malignancy. There were two exceptions, Cases 5 and 7, both of whom had undifferentiated round cell liposarcoma, type III. Yet in Case 5, the primary tumor of the foot had been present for 22 years, and the patient died one year after the first operation. On the other hand, in Case 7, the tumor of the thigh, including one recurrence (Fig. 3b) had been present for 6 years prior to the second operation and supervoltage irradiation. Subsequently the patient has been free of tumor for 5 years. Aside from these exceptions, the shortest life histories occurred in highly malignant tumors, and the longest in low grade tumors.

Complications. Supervoltage irradiation in large doses does not produce the severe initial skin reactions that are encountered with conventional therapy but does produce at a later time dense fibrosis of the subcutaneous tissues. The overlying skin secondarily becomes devascularized and is prone to late necrosis.

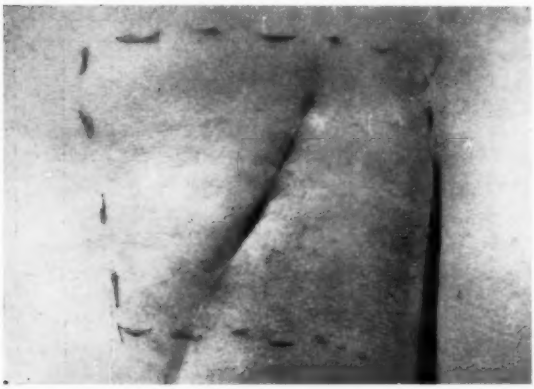


Fig. 8. Case 3. Intact skin of left buttock and moderate subcutaneous fibrosis three years after a large tissue dose of 8 988 rads in 31 days with 2 MV roentgen irradiation using the rotation technique.

In almost all cases where the tissue dose near the surface skin exceeded 5 000 rads, dense subcutaneous and muscle fibrosis developed. In many patients this was not severe or incapacitating. Fig. 8 shows the left buttock of a patient 3 years after a tumor dose of 9 000 rads in 31 days (Case 3) delivered with 2 MV roentgen radiation using a 270° rotation technique. The lesion was arrested and the appearance of the skin remained unchanged four and a half years after therapy when the patient died from metastatic disease.

In other cases the consequences were more serious. Fig. 9 shows the left thigh of a patient (Case 8) two years after a tumor dose of 9 360 rads in 49 days delivered through anterior and posterior portals with 2 MV roentgen rays. Approximately a year and a half later, there occurred a spiral fracture of the lower end of the femur following minimal trauma. There is now no evidence of neoplasm four years after treatment.

Fig. 10 shows the left knee of another patient (Case 7) five years after a tumor dose of 9 200 rads in 39 days delivered with 2 MV roentgen rays through two opposing portals. There is a large necrotic ulcer on the lateral aspect of the leg which had been produced by contact with a chemical irritant. A similar smaller ulcer on the anterior aspect of the thigh had previously healed. There is no evidence of tumor to date, five years after therapy. Based on our experience with other lesions of the lower extremities (FRIEDMAN & EGAN), this incidence of radionecrosis was higher than anticipated; otherwise we would consider this type of risk prohibitive.

Fig. 9. Case 8. Left thigh two years after a tissue dose of 9 360 rads in 49 days delivered through two opposing portals with 2 MV roentgen. Three and a half years after irradiation the lower femur sustained a spiral fracture following minimal trauma, which is now healing.

Fig. 10. Case 7. Type III undifferentiated round cell liposarcoma (Cf. fig. 3b). Large radiation ulcer on the lateral aspect of left thigh occurring 5 years after a tissue dose of 9 200 rads in 39 days, due to contact with an irritating 'home remedy'. A similar smaller ulcer, barely visible on the anteromedial aspect, had healed several years previously.

Conclusions

1. The belief in some radiotherapeutic circles, that liposarcoma is occasionally moderately radiosensitive and even curable, may be true but it has not been well documented with accurate details of radiation dosage in the published reports. We have therefore analyzed the response to supervoltage (2 MV) roentgen treatment of fifteen lesions in twelve patients.

2. The tumors were classified into three groups, as suggested by A. P. Stout, according to the histologic degree of malignancy. This type of grading is difficult with liposarcoma because of the proneness of each tumor to contain several histologic types. Nevertheless the clinical behaviour tended to parallel the major histologic type.

3. In order to arrest liposarcoma with irradiation in our series, tumor doses of approximately 9,000 rads in 30 to 50 days were given. These large doses to the lower extremity resulted in a high incidence of radiation injury.

Smaller doses of 4,000 to 7,000 rads arrested some lesions for several month to one year. The patients died of metastasis so that we could not validate thi dosage range for long term effects. Nevertheless, based on these experience and personal communication with other radiotherapists, it is possible tha tumor doses of 6,000 to 7,000 rads might cure an occasional well differentiate myxoid liposarcoma, type I, without producing serious radiation injury.

4. A useful palliative dose for individual lesions in a case of incurabl liposarcoma is 3,000 to 4,000 rads in 20 days to 30 days.

5. Liposarcoma is another exception to the law of Bergonie-Tribondea in that the slowly growing, low grade malignancy, well differentiated type is relatively radiosensitive; whereas the rapidly growing, highly malignan round cell type III is radioresistant.

6. Liposarcoma often grows slowly and has a long life history, even wit inadequate treatment. Although the more differentiated histologic type tend to have the longer life history, there are occasional exceptions. In many instances a five year follow-up period may be too short to define a cure.

7. Irradiation can play an important role in the retardation and arrest of many liposarcomas. This review of 15 lesions in 12 patients is not offered as a definitive study, but to supplement the very meager dose and response data in the literature.

SUMMARY

The response to supervoltage roentgen treatment (2 MV) of fifteen liposarcomas, in twelve patients, was analyzed, the tumours being classified according to the histologic degree of malignancy. It was found, paradoxically, that the differentiated liposarcomas were more radiosensitive than the undifferentiated lesions. Irradiation can only occasionally contribute towards a cure. The tumour lethal dose ranges from 6 000 to 9 000 rads in 30 to 50 days, and a useful palliative dose is 3,000 to 4,000 rads in 20 to 30 days. The prolonged natural life history of many liposarcomas requires a 10-year-follow-up for evaluation of the treatment.

ZUSAMMENFASSUNG

Das Ergebnis nach Supervoltage Röntgen Bestrahlung (2 MV) von 15 Liposarkomen bei 12 Patienten wurde analysiert, wobei die Tumore histologisch mit Hinsicht auf ihre Malignität klassifiziert wurden. Es wurde widersinnig gefunden, dass die differenzierten Liposarkome mehr radiosensitiv sind als die undifferenzierten. Bestrahlung kann nur gelegentlich zu einer Heilung beitragen. Die Tumor-letale Dosis rangiert von 6,000 bis 9,000 rad in 30—50 Tagen, eine nützliche palliative Dosis von 3,000 bis 4,000 rad in 20—30 Tagen. Die verlängerte natürliche Lebensgeschichte vieler Liposarkome erfordert eine 10-jährige Nachkontrolle um den Erfolg der Behandlung beurteilen zu können.

RÉSUMÉ

Les auteurs analysent l'effet du traitement par les supervoltages (2 MV Röntgen) sur quinze liposarcomes chez douze malades; les tumeurs ont été classées d'après leur degré de malignité histologique. Les auteurs ont constaté que, paradoxalement, les liposarcomes différenciés ont été plus radiosensibles que les lésions indifférenciées. L'irradiation ne contribue que rarement à la guérison. La dose léthale tumorale va de 6,000 à 9,000 rad en 30 à 50 jours, et la dose palliative utile est de 3,000 à 4,000 rad en 20 à 30 jours. La longue survie spontanée de beaucoup de liposarcomes rend nécessaire une surveillance de 10 ans pour juger l'efficacité du traitement.

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BOOK REVIEW

STRAHLENBELASTUNG UND STRAHLENSCHUTZ IN DER PÄDIATRISCHEN RÖNTGENDIAGNOSTIK. Von Kurt Hartung. Georg Thieme, Stuttgart 1959. 128 Seiten, 26 Abbildungen, 97 Tabellen. Price: DM 18. 60.

The purpose of this book, which according to the author is intended to be a »Habilitationsschrift", is to give a survey of the general biologic effects of ionizing radiation, and in the light of this, to present from his own experience a determination of the radiation doses, especially the gonad doses, in radiodiagnostic investigations in children. The subject possesses great general interest, and all new contributions likely to increase our knowledge in this field are welcome.

In the introductory sections the author describes various forms of radiation doses as well as the recommendations advanced at international radiation conferences. The biologic factors of especial interest in infants and young children are also given some attention. In the following sections different methods of dose calculation are treated, and skin doses and gonad doses in connection with different forms of exposure and at fluoroscopy are compared on the basis of over 3 000 determinations. In conclusion the author discusses the possibilities of achieving protection against radiation damage in children.

Unfortunately, it cannot be denied that the value of the work is lessened by inadvertencies, not only on minor points but also to some extent on questions serious enough to affect the general conclusions. The technique does not seem to be wholly unimpeachable and is difficult to follow in some of its details. It appears from Table 66, for instance, which is intended to demonstrate the size of the entrance doses with different amounts of current, that the milliampèremeter must have been subject to an inherent error amounting to at least 20 per cent. The values given in Table 67, showing how the entrance doses are dependent on the voltage, are of little use as the filter value is not stated. In the postmortem determinations of the gonad dose in girls, the measuring chamber was placed in the rectum instead of over the ovaries. The method of determining purely physical radiation variations in the postmortem experiments is also surprising. Field sizes and filter values are not given for the different examinations, and the significance of 'the effective values without Pb' is not sufficiently clear from the definitions. It is difficult to understand why the author recommends the use of the lowest possible kV and mA. The fact that examinations involving direct irradiation of the gonads are so sparsely represented is naturally a disadvantage. No information on the radiation doses in connection with urethrocystography seems to have been obtained. The majority of the examinations were carried out within the 50—60 kV range, a practice which is in many respects out-of-date in modern roentgen departments.

It should also be pointed out that Crow's investigations into the curtailment of life among radiologists have proved to be statistically unsatisfactory and do not permit definite conclusions to be drawn. Furthermore, contrary to the author's assertion, the mechanism in acute radiation damage has not yet been wholly cleared up.

The author's suggestions as to measures to achieve increased protection against radiation are reasonable but, judging from the illustrations, a suitably small primary diaphragm was not always employed.

Ulf Ruche